

<https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club>

The weekly Clinical Journal Club by Dr. Friedrich C. Luft

Usually every Wednesday 17:00 - 18:00



Klinische Forschung

Experimental and Clinical Research Center (ECRC) von MDC und Charité

Als gemeinsame Einrichtung von MDC und Charité fördert das Experimental and Clinical Research Center die Zusammenarbeit zwischen Grundlagenwissenschaftlern und klinischen Forschern. Hier werden neue Ansätze für Diagnose, Prävention und Therapie von Herz-Kreislauf- und Stoffwechselerkrankungen, Krebs sowie neurologischen Erkrankungen entwickelt und zeitnah am Patienten eingesetzt. Sie sind eingeladen, um uns beizutreten. [Bewerben Sie sich!](#)

An 18-year-old man presented with a 2-day history of fever, vomiting, and diarrhea. Three weeks before presentation, he had fallen into a canal. Physical exam was notable for the findings shown in the image. Laboratory studies showed acute kidney injury and elevations in aminotransferase and total bilirubin levels. What is the most likely diagnosis?



Acute hemorrhagic conjunctivitis

Ebola hemorrhagic fever

Giardiasis

Leptospirosis



Subarachnoid hemorrhage

Correct!

Leptospirosis manifesting as fever, jaundice, renal failure, and hemorrhage was suspected on the basis of the patient's classic presentation (including the subconjunctival bleeding) and exposure to water with probable contamination by rodent urine. Empirical treatment with intravenous penicillin was initiated. Serum nucleic acid amplification testing identified leptospira species of the serogroup icterohaemorrhagiae. At follow-up 3 weeks later, his symptoms, subconjunctival hemorrhage, and liver and kidney injury had resolved.

Acute hemorrhagic conjunctivitis (AHC) is a derivative of the highly contagious conjunctivitis virus, otherwise known as pink eye. Symptoms include excessively red, swollen eyes as well as subconjunctival hemorrhaging. Currently, there is no known treatment and patients are required to merely endure the symptoms while the virus runs its five- to seven-day course. While it was first identified in Ghana, the virus has now been seen in China, India, Egypt, Cuba, Singapore, Taiwan, Japan, Pakistan, Thailand, and the United States. There are three main viruses that have been studied and confirmed as the agents responsible for AHC, including **enterovirus 70, coxsackievirus A24 variant (CA24v) and adenovirus 11**



Ebola virus disease (EVD), formerly known as Ebola haemorrhagic fever, is a rare but severe, often fatal illness in humans.

The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission.

The average EVD case fatality rate is around 50%. Case fatality rates have varied from 25% to 90% in past outbreaks.



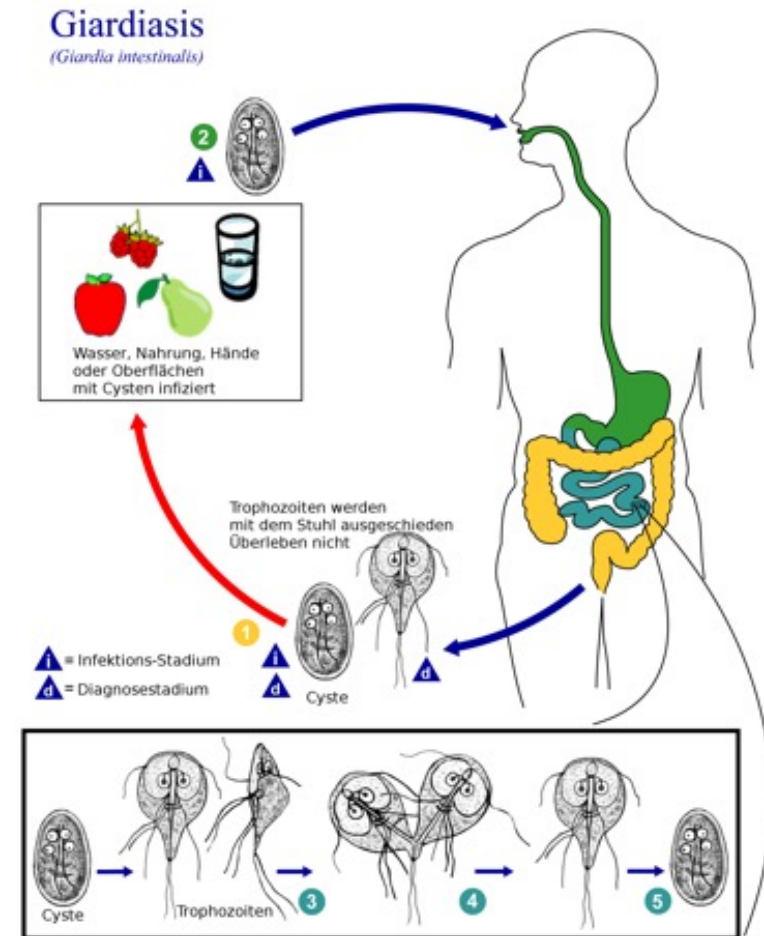
Die **Giardiasis** (Syn.: Lambliasis, Lambliegenruhr) ist eine durch das Geißeltierchen *Giardia intestinalis* (Genotyp A und B) hervorgerufene Erkrankung des Menschen. Auch andere Säugetiere können an einer Giardiose erkranken, wobei hier andere Genotypen als Auslöser ermittelt wurden. Die beim Menschen vorkommenden Genotypen können auch bei Hunden (→ Giardiose des Hundes) und Katzen eine Erkrankung auslösen.



Notice that:

There is redness around the nasal passage; subject reported general allergic symptoms.

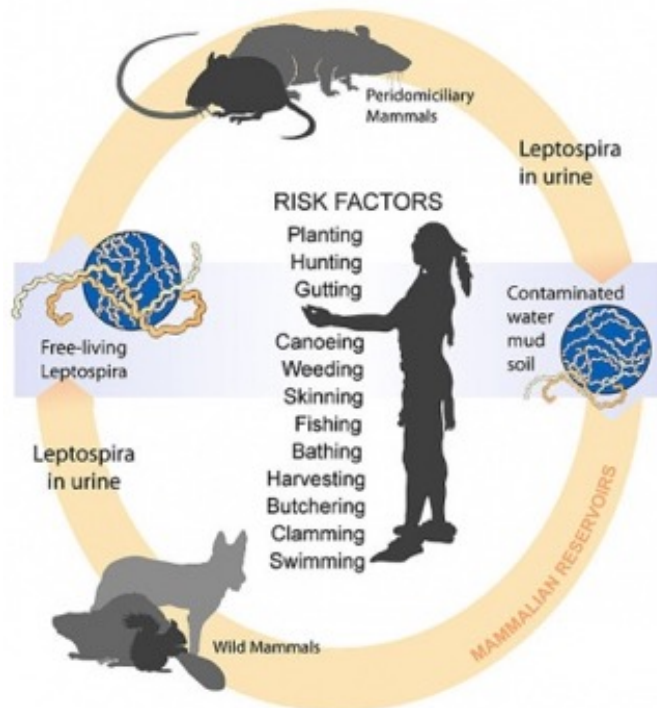
The image of the flash appears as a horizontal white blob in the pupil. That part of the eye is obviously sloping away from the viewer. Two identical flash images appear in the inflamed conjunctiva, indicating similar angles of incidence there due to the swelling. In a normal eye, the flash image in the pupil would be the only one.



Die **Leptospirose** ist eine weltweit vorkommende Zoonose, die von pathogenen Bakterien der Gattung *Leptospira* hervorgerufen wird. Das Spektrum an Manifestationen reicht von einer asymptomatischen Infektion bis hin zum fulminanten Verlauf, den man als Morbus Weil bezeichnet. Leptospiren sind dünne, spiralförmige und bewegliche Bakterien. Sie zählen zu den Spirochäten aus der Ordnung Spirochaetales (Familie Leptospiraceae).

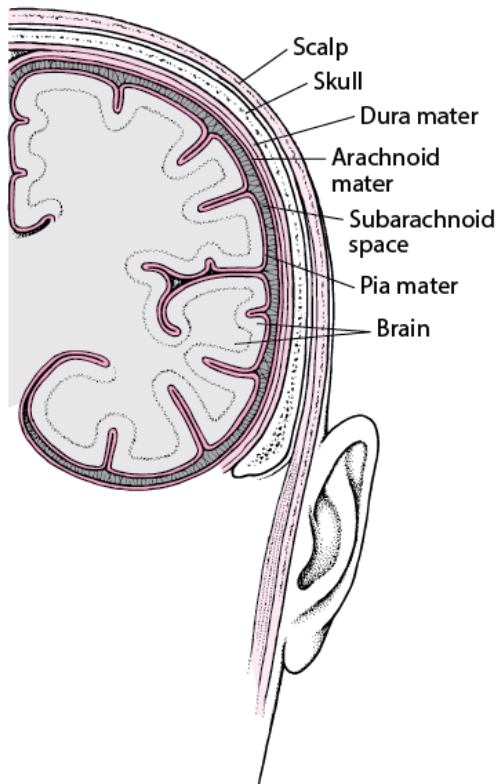
Derzeit (2021) werden 10 pathogene Arten (z.B. *Leptospira interrogans*, *Leptospira weilli*), fünf intermediär pathogene (z.B. *Leptospira broomii*) und sieben nicht-pathogene, saprophytäre Arten (z.B. *Leptospira biflexa*) unterschieden. Anhand der Antigenzusammensetzung werden 26 Serogruppen mit über 250 Serovare differenziert.

Leptospiren gelangen über Hautverletzungen oder die Schleimhäute (v.a. Konjunktiva, Mundschleimhaut) in den Organismus und breiten sich hämatogen in alle Organe aus (leptospirämische Phase). In dieser Inkubationsperiode können sie aus dem Blut isoliert werden. Die Leptospiren hemmen mithilfe des Bindungsfaktor H auf ihrer Oberfläche das Komplementsystem. Außerdem sind sie resistent gegenüber der Abtötung durch Phagozyten.

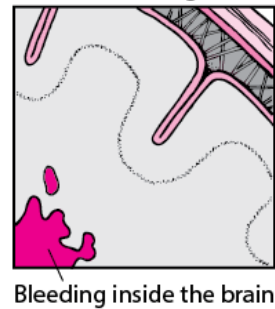


Teaching NeurolImages: Raccoon eye in subarachnoid hemorrhage

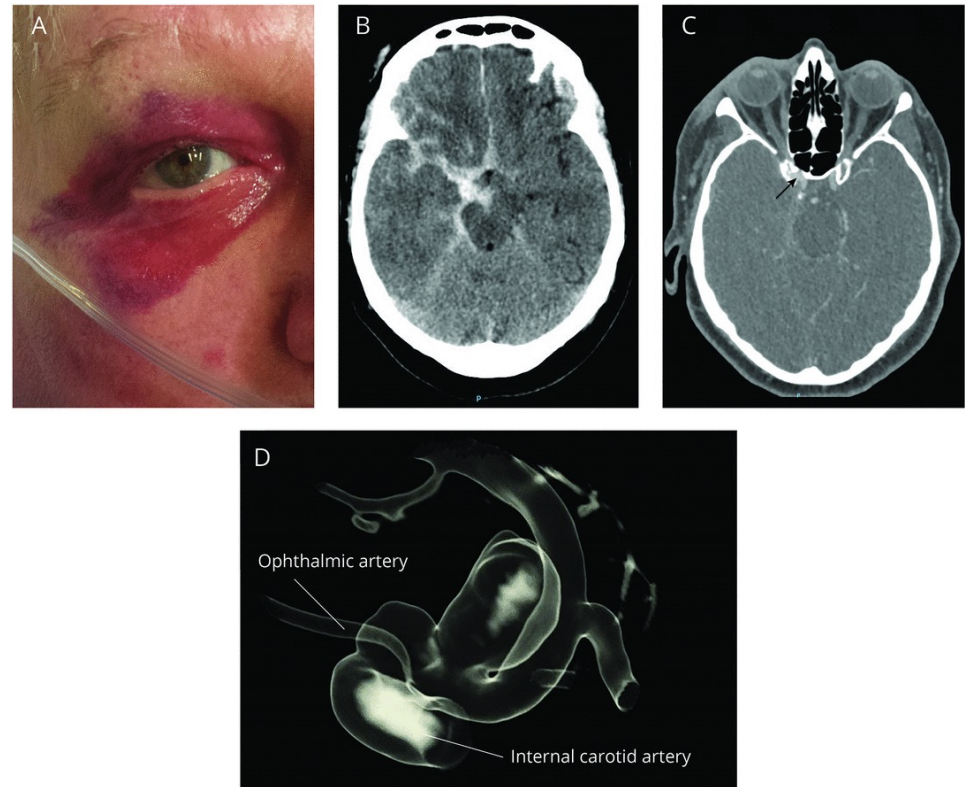
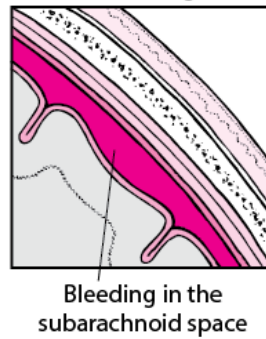
Cross Section of the Brain



Intracerebral Hemorrhage



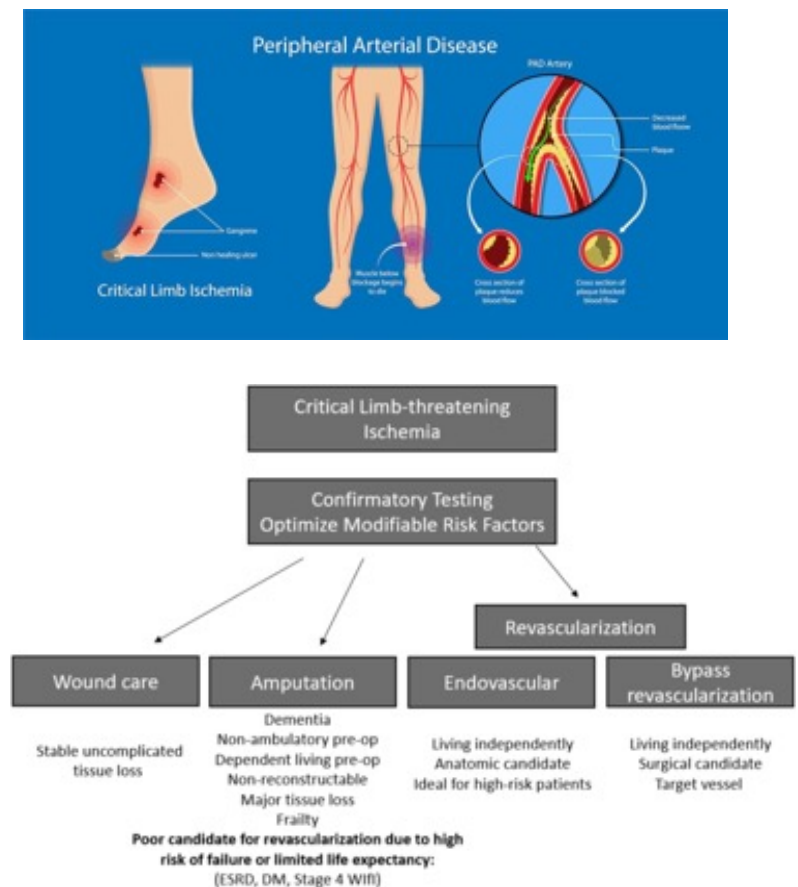
Subarachnoid Hemorrhage



CT angiography showed subarachnoid hemorrhage (SAH) from a right ophthalmic artery aneurysm

Chronic limb threatening ischemia (CLTI), also known as critical limb ischemia (CLI), is an advanced stage of peripheral artery disease (PAD). It is defined as ischemic rest pain, arterial insufficiency ulcers, and gangrene. The latter two conditions are jointly referred to as tissue loss, reflecting the development of surface damage to the limb tissue due to the most severe stage of ischemia. Compared to the other manifestation of PAD, intermittent claudication, CLI has a negative prognosis within a year after the initial diagnosis, with **1-year amputation rates of approximately 12% and mortality of 50% at 5 years and 70% at 10 years.**

CLI was conceived to identify patients at high-risk for major amputation, but the increasing prevalence of diabetes mellitus has led to a broader conception of limb threat that includes the risk of amputation associated with severely infected and non-healing wounds. Treatment mirrors that of other symptoms of peripheral artery disease, and includes modifying risk factors, revascularization via vascular bypass or angioplasty, and in the case of tissue loss, wound debridement.

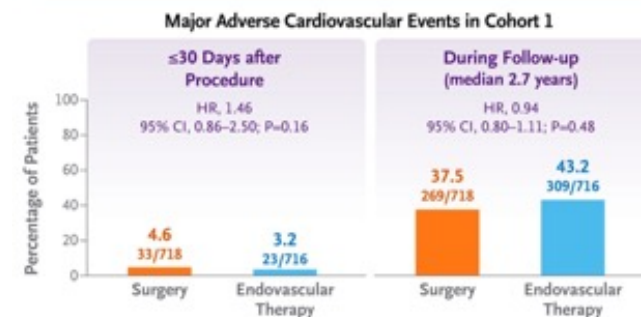
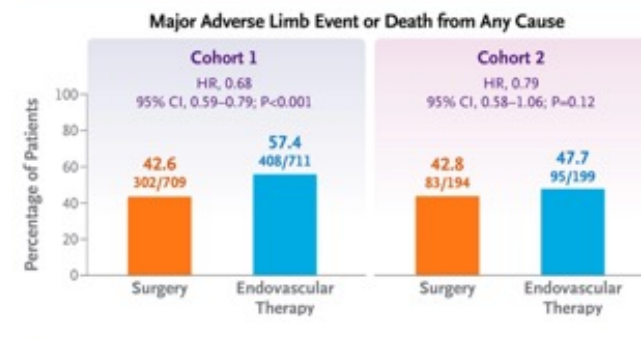
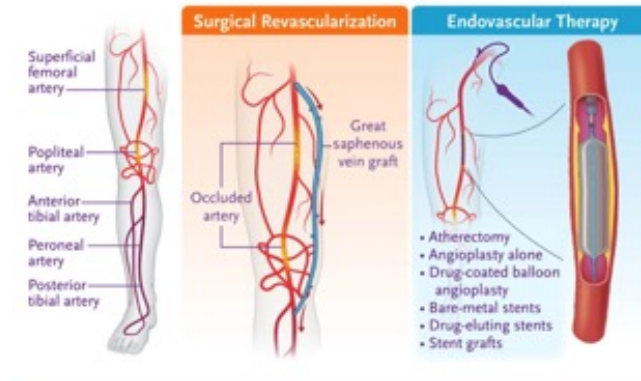


Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia

Patients with chronic limb-threatening ischemia (CLTI) require revascularization to improve limb perfusion and thereby limit the risk of amputation. It is uncertain whether an initial strategy of endovascular therapy or surgical revascularization for CLTI is superior for improving limb outcomes. In this international, randomized trial, we enrolled 1830 patients with CLTI and infrainguinal peripheral artery disease in **two parallel-cohort trials**. Patients who had a single segment of great saphenous vein that could be used for surgery were assigned to cohort 1. Patients who needed an alternative bypass conduit were assigned to cohort 2. The primary outcome was a composite of a major adverse limb event — which was defined as **amputation above the ankle** or **a major limb reintervention** (a new bypass graft or graft revision, thrombectomy, or thrombolysis) — or death from any cause.

LIMITATIONS AND REMAINING QUESTIONS

- Study results may have been influenced by selection or operator bias as a consequence of the pragmatic trial design and implementation.
- Patient suitability for procedures was determined locally and varied according to study site and individual investigator.
- Enrollment targets were not met for patients overall and for women.



CONCLUSIONS

Among patients with CLTI who had a great saphenous vein adequate for surgical revascularization, clinical outcomes with an initial treatment of surgery were superior to those with endovascular therapy; however, in patients who required an alternative bypass conduit, outcomes were similar with the two procedures.

Trial Inclusion and Exclusion Criteria

Patients with CLTI must meet the following inclusion and exclusion criteria in order to be enrolled in the study:

Inclusion criteria (all must be met for eligibility):

- 1) Male or female, age 18 years or older.
- 2) Infrainguinal PAD (occlusive disease of the arteries below the inguinal ligament).
- 3) CLTI, defined as arterial insufficiency with gangrene, non-healing ischemic ulcer, or rest pain consistent with Rutherford categories 4-6.
- 4) Candidate for both endovascular and open infrainguinal revascularization as judged by the treating investigators (see Manual of Operations for guidelines on decision-making).
- 5) Adequate aortoiliac inflow, either already present at baseline or to be established prior to or at the time of the index revascularization.*
- 6) Adequate popliteal, tibial or pedal revascularization target defined as an infrainguinal arterial segment distal to the area of stenosis/occlusion which can support a distal anastomosis of a surgical bypass.
- 7) Willingness to comply with protocol, attend follow-up appointments, complete all study assessments, and provide written informed consent.

Randomization

Patients were enrolled into one of two parallel-trial cohorts according to prerandomization duplex ultrasonography of the right and left great saphenous veins. Within each cohort, eligible patients were stratified according to clinical criteria (ischemic rest pain or tissue loss) and anatomical criteria (presence or absence of considerable infrapopliteal arterial occlusive disease) with the use of permuted randomized blocks. The patients were then randomly assigned in a 1:1 ratio to receive surgical or endovascular treatment.

Outcomes

The primary outcome was a composite of major adverse limb events or death from any cause. A major adverse limb event was defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis).

Exclusion criteria (none can be met for eligibility):

- 1) Presence of a popliteal aneurysm (>2 cm) in the index limb.
- 2) Life expectancy of less than 2 years due to reasons other than PAD.
- 3) Excessive risk for surgical bypass (as determined by the operating surgeon and the CLI Team).
- 4) Planned above-ankle amputation on ipsilateral limb within 4 weeks of index procedure.
- 5) Active vasculitis, Buerger's disease, or acute limb-threatening ischemia.
- 6) Any prior index limb infrainguinal stenting or stent grafting associated with significant restenosis within 1 cm of the stent or stent-graft, unless the occlusion/restenosis site is outside the intended treatment zone (i.e., a tibial vessel that is not currently intended to be revascularized as a part of the treatment for CLTI).
- 7) Any of the following procedures performed on the index limb within 3 months prior to enrollment:
 - a. Infrainguinal balloon angioplasty, atherectomy, stent, or stentgraft;
 - b. Infrainguinal bypass with either venous or prosthetic conduit
- 8) Open surgical inflow procedure (aortofemoral, axillofemoral, iliofemoral, thoracofemoral or femorofemoral bypass) within 6 weeks prior to enrollment
- 9) Current chemotherapy or radiation therapy.
- 10) Absolute contraindication to iodinated contrast due to prior near-fatal anaphylactoid reaction (laryngospasm, bronchospasm, cardiorespiratory collapse, or equivalent) which would preclude patient participation in angiographic procedures.
- 11) Pregnancy or lactation.
- 12) Administration of an investigational drug for PAD within 30 days of randomization.
- 13) Participation in a clinical trial (except observational studies) within the previous 30 days.
- 14) Prior enrollment or randomization into BEST-CLI.

Synthetic materials for fabricating vascular grafts include biodegradable polymers such as polyglycolic acids (PGA, PLA, PLGA), or non-biodegradable polymers such as polyurethanes

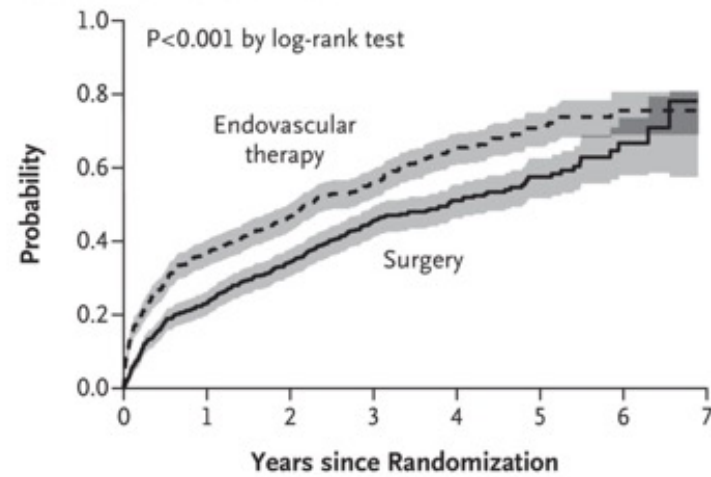
Characteristic	Saphenous vein		Cohort 1		„Plastic“		Cohort 2	
	Overall (N = 1434)		Surgery (N = 718)	Endovascular Therapy (N = 716)	Overall (N = 396)		Surgery (N = 197)	Endovascular Therapy (N = 199)
Demographic								
Age — yr	66.9±9.9		66.9±9.8	67.0±10.0	68.6±9.2		68.4±8.8	68.8±9.6
Female sex — no./total no. (%)	408/1434 (28.5)		201/718 (28.0)	207/716 (28.9)	111/396 (28.0)		56/197 (28.4)	55/199 (27.6)
Race or ethnic group — no./total no. (%)†								
White	1028/1423 (72.2)		500/711 (70.3)	528/712 (74.2)	275/390 (70.5)		143/194 (73.7)	132/196 (67.3)
Black	275/1423 (19.3)		156/711 (21.9)	119/712 (16.7)	96/390 (24.6)		40/194 (20.6)	56/196 (28.6)
Asian	20/1423 (1.4)		13/711 (1.8)	7/712 (1.0)	2/390 (0.5)		2/194 (1.0)	0/196
Other	100/1423 (7.0)		42/711 (5.9)	58/712 (8.1)	17/390 (4.4)		9/194 (4.6)	8/196 (4.1)
Hispanic	187/1433 (13.0)		82/717 (11.4)	105/716 (14.7)	53/396 (13.4)		28/197 (14.2)	25/199 (12.6)
Medical history								
Body-mass index‡	28.2±6.0		28.2±6.3	28.3±5.8	26.9±5.7		26.8±5.1	27.0±6.2
Coexisting condition — no./total no. (%)								
Hypertension	1238/1424 (86.9)		620/712 (87.1)	618/712 (86.8)	350/395 (88.6)		171/196 (87.2)	179/199 (89.9)
Hyperlipidemia	1041/1423 (73.2)		521/712 (73.2)	520/711 (73.1)	299/395 (75.7)		147/196 (75.0)	152/199 (76.4)
Diabetes	1023/1424 (71.8)		513/712 (72.1)	510/712 (71.6)	238/395 (60.3)		122/196 (62.2)	116/199 (58.3)
Current smoking	509/1424 (35.7)		264/712 (37.1)	245/712 (34.4)	140/395 (35.4)		69/196 (35.2)	71/199 (35.7)
Coronary artery disease	617/1424 (43.3)		301/712 (42.3)	316/712 (44.4)	204/395 (51.6)		97/196 (49.5)	107/199 (53.8)
Congestive heart failure	79/1422 (5.6)		38/711 (5.3)	41/711 (5.8)	27/395 (6.8)		12/196 (6.1)	15/199 (7.5)
Stroke	190/1424 (13.3)		91/712 (12.8)	99/712 (13.9)	62/395 (15.7)		38/196 (19.4)	24/199 (12.1)
Chronic obstructive pulmonary disease	208/1424 (14.6)		100/712 (14.0)	108/712 (15.2)	69/395 (17.5)		34/196 (17.3)	35/199 (17.6)
End-stage kidney disease	151/1423 (10.6)		67/712 (9.4)	84/711 (11.8)	45/395 (11.4)		25/196 (12.8)	20/199 (10.1)
Medication								
Statin — no./total no. (%)	1001/1424 (70.3)		503/713 (70.5)	498/711 (70.0)	307/394 (77.9)		153/195 (78.5)	154/199 (77.4)
Aspirin — no./total no. (%)	953/1424 (66.9)		476/713 (66.8)	477/711 (67.1)	280/394 (71.1)		139/195 (71.3)	141/199 (70.9)
Clopidogrel — no./total no. (%)	312/1424 (21.9)		137/713 (19.2)	175/711 (24.6)	97/394 (24.6)		55/195 (28.2)	42/199 (21.1)
Prasugrel — no./total no. (%)	5/1424 (0.4)		2/713 (0.3)	3/711 (0.4)	1/394 (0.3)		0/195	1/199 (0.5)
Ticagrelor — no./total no. (%)	10/1424 (0.7)		4/713 (0.6)	6/711 (0.8)	4/394 (1.0)		0/195	4/199 (2.0)
Direct-acting oral anticoagulant — no./total no. (%)	55/1424 (3.9)		27/713 (3.8)	28/711 (3.9)	22/394 (5.6)		9/195 (4.6)	13/199 (6.5)
Warfarin — no./total no. (%)	93/1424 (6.5)		46/713 (6.5)	47/711 (6.6)	31/394 (7.9)		12/195 (6.2)	19/199 (9.5)
Previous intervention								
Tobacco cessation — no./total no. (%)	97/1424 (6.8)		49/712 (6.9)	48/712 (6.7)	26/395 (6.6)		11/196 (5.6)	15/199 (7.5)
Infrainguinal revascularization of index limb — no./total no. (%)	77/1423 (5.4)		40/711 (5.6)	37/712 (5.2)	40/393 (10.2)		20/194 (10.3)	20/199 (10.1)
Limb status								
Ankle–brachial index in index limb§	0.58±0.32		0.58±0.31	0.59±0.34	0.54±0.30		0.53±0.27	0.54±0.32
Ankle pressure — mm Hg¶	84.9±47.7		85.2±46.2	84.5±49.2	81.3±49.6		80.4±47.3	82.2±51.8
Toe pressure — mm Hg	36.3±25.7		36.5±27.7	36.1±23.5	31.0±21.7		37.0±23.5	25.5±18.4

Efficacy and Safety Outcomes in Cohort 1.

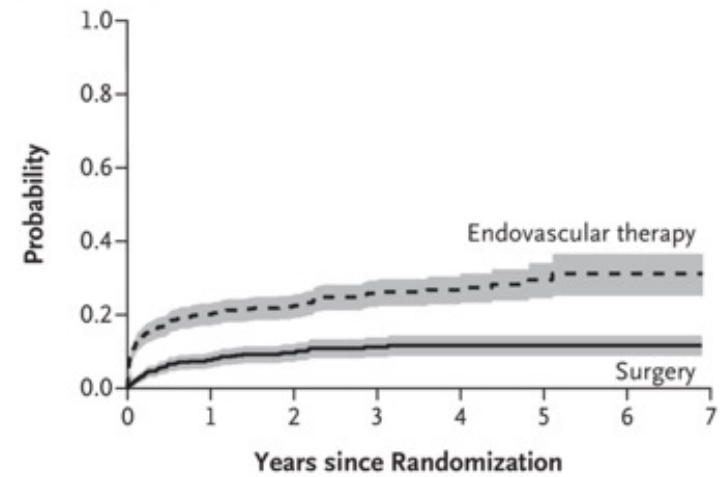
Outcome	Surgery	Endovascular Therapy	Hazard Ratio (95% CI) [†]	P Value
Efficacy				
Primary outcome: major adverse limb event or death from any cause — no./total no. (%) [‡]	302/709 (42.6)	408/711 (57.4)	0.68 (0.59–0.79)	<0.001
Secondary outcomes — no./total no. (%)				
Death from any cause	234/709 (33.0)	267/711 (37.6)	0.98 (0.82–1.17)	
Above-ankle amputation of the index limb	74/709 (10.4)	106/711 (14.9)	0.73 (0.54–0.98)	
Intervention in index limb				
Major	65/709 (9.2)	167/711 (23.5)	0.35 (0.27–0.47)	
Minor	205/718 (28.6)	237/716 (33.1)	0.85 (0.70–1.02)	
Perioperative death [§]	12/687 (1.7)	9/708 (1.3)	1.54 (0.64–3.68)	
Major adverse limb event or perioperative death	139/687 (20.2)	246/708 (34.7)	0.53 (0.43–0.65)	
Myocardial infarction	75/718 (10.4)	85/716 (11.9)	0.97 (0.71–1.33)	
Stroke	39/718 (5.4)	44/716 (6.1)	0.93 (0.60–1.43)	
Safety				
Major adverse cardiovascular event — no. of patients with ≥1 event/total no. of patients (%)				
Event ≤30 days after procedure [¶]	33/718 (4.6)	23/716 (3.2)	1.46 (0.86–2.50)	0.16
Event during follow-up	269/718 (37.5)	309/716 (43.2)	0.94 (0.80–1.11)	0.48
Serious adverse event				
Event occurred ≤30 days after index procedure — no. of patients with ≥1 event/total no. of patients (%)	244/718 (34.0)	226/716 (31.6)		0.34
No. of events ≤30 days after index procedure	427	379		0.10
No. of patients with ≥1 event/total no. of patients (%)	590/718 (82.2)	614/716 (85.8)		0.07
No. of events during follow-up	3141	3468		<0.001
Technical success of index procedure — no./total no. (%) ^{**}	651/662 (98.3)	596/704 (84.7)		
Length of hospital stay after index procedure ^{††}				
No. of days	7.5±6.2	5.9±7.3		
Median no. of days (IQR)	6 (4–9)	3 (1–8)		

Kaplan–Meier Curves of the Primary Outcome and Its Components in Cohort 1.

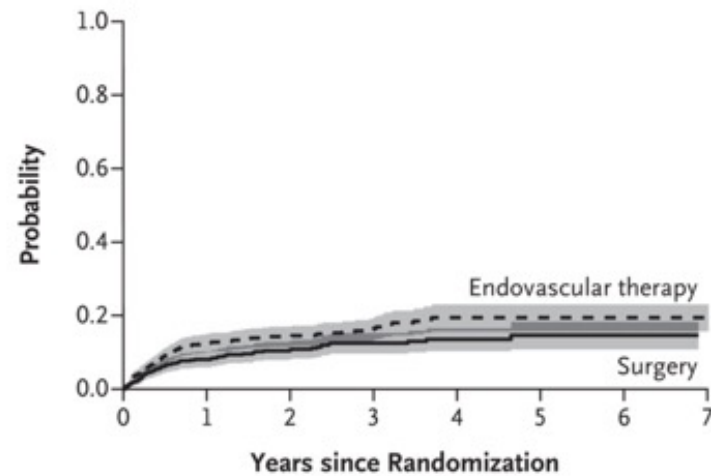
Major Adverse Limb Events or Death



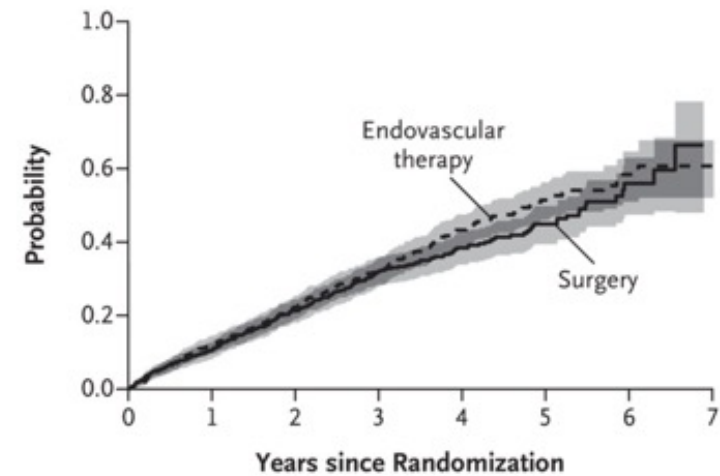
B Major Reintervention



Above-Ankle Amputation



D Death



Cohort 2

Index Procedure

The technical success was 100% in the surgical group and 80.6% in the endovascular group. Of the 37 early cases of technical failure in the endovascular group, 26 patients underwent surgical bypass within 30 days.

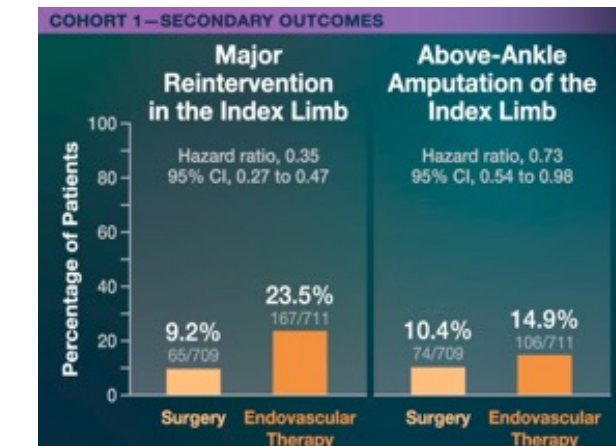
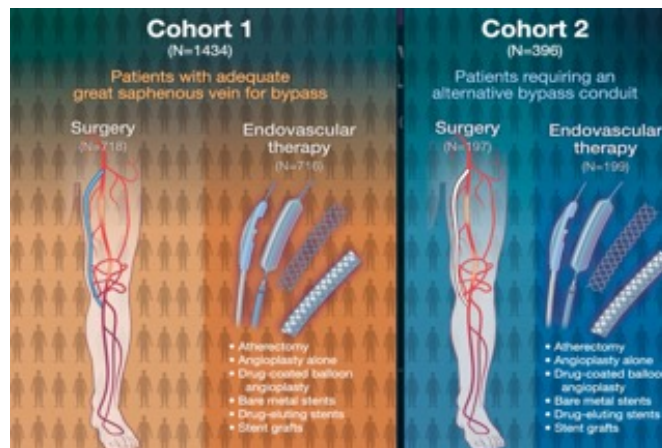
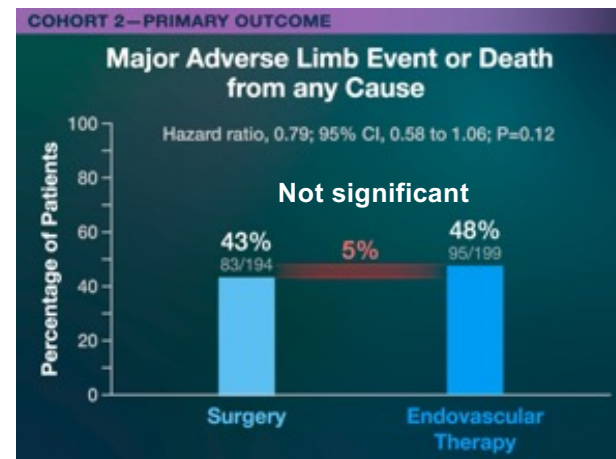
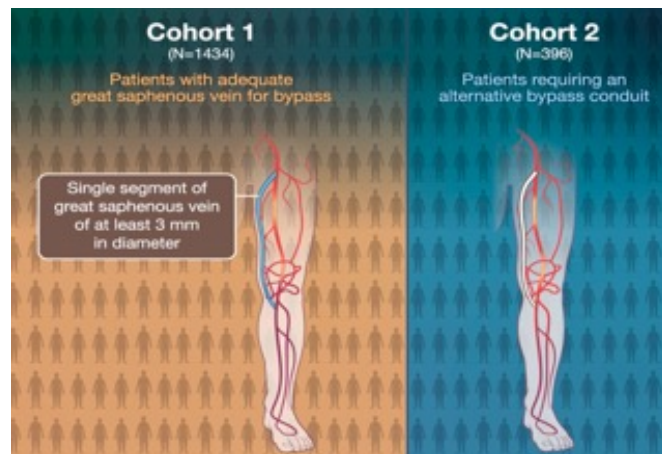
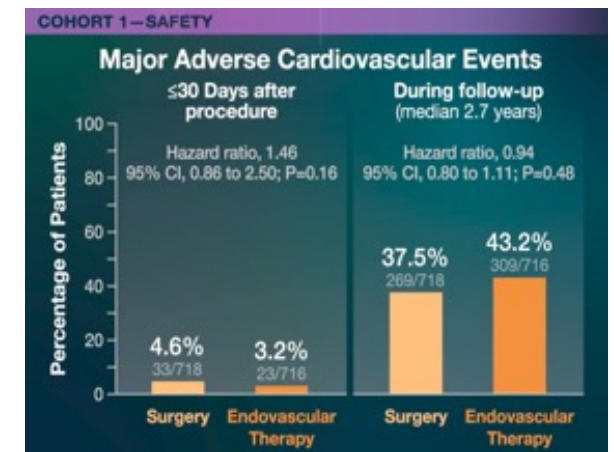
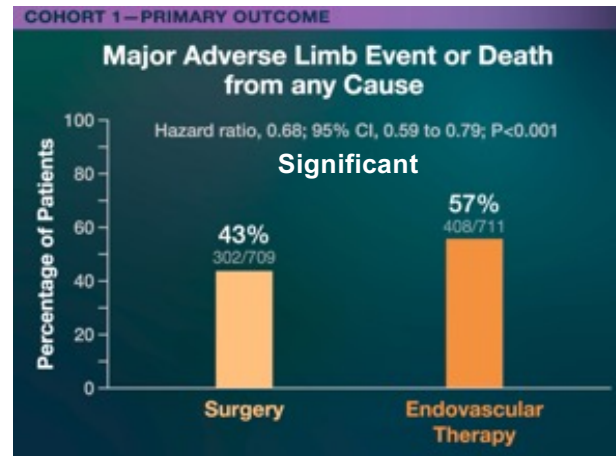
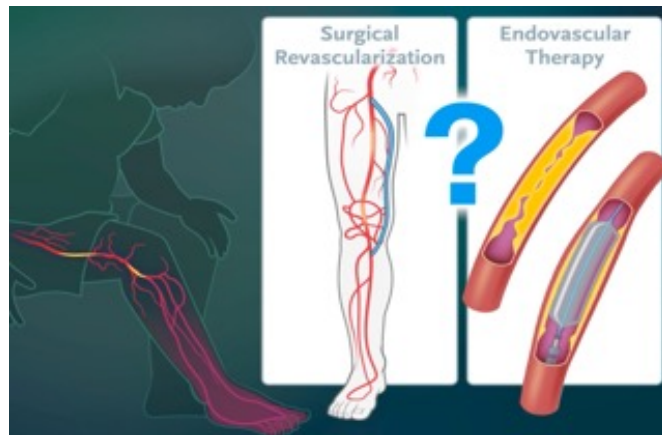
In the surgical group, 105 femoral–popliteal, 86 femoral–tibial or pedal, and 18 popliteal–tibial or pedal bypasses were performed. There were 48 bypasses involving alternative autogenous veins and 119 bypasses involving a prosthetic conduit. In 19% of cases, the surgeon unexpectedly identified a single segment of great saphenous vein that was suitable for bypass surgery. Among the endovascular interventions, 133 were performed on the superficial femoral artery, 114 on the popliteal artery, and 86 on the tibial or pedal arteries.

Outcomes

The primary outcome of major adverse limb events or death from any cause occurred in 83 of 194 patients (42.8%) in the surgical group and in 95 of 199 patients (47.7%) in the endovascular group (hazard ratio, 0.79; 95% CI, 0.58 to 1.06; $P=0.12$). The time until a major reintervention favored the surgical group (hazard ratio, 0.47; 95% CI, 0.29 to 0.76). There were no material between-group differences in the time until above-ankle amputation or death from any cause (Fig. S3C and S3D and Tables S9 and S10). Similar results were obtained across subgroups (Fig. S4) and in the per-protocol and as-treated analyses of the primary outcome. There was no material difference between the surgical group and the endovascular group regarding the incidence of new or recurrent CLTI events (incidence rate ratio, 0.87; 95% CI, 0.64 to 1.17).

Adverse Events

Major adverse limb events occurred in 13 of 396 patients (3.3%) from the date of randomization through 30 days after the index procedure and in 124 of 396 patients (31.3%) through the end of the trial. There were no material between-group differences in the time until a major adverse limb event overall or at 30 days or until myocardial infarction or stroke. The median length of hospital stay was longer in the surgical group.

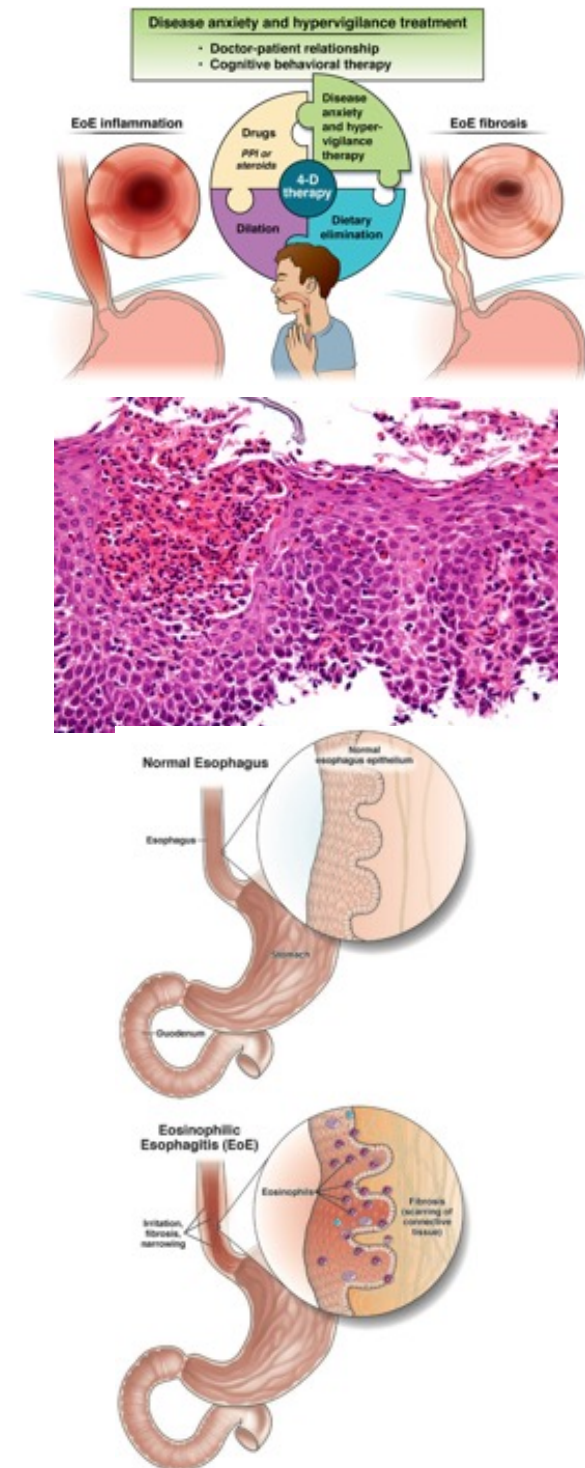


Eosinophilic esophagitis (EoE) is

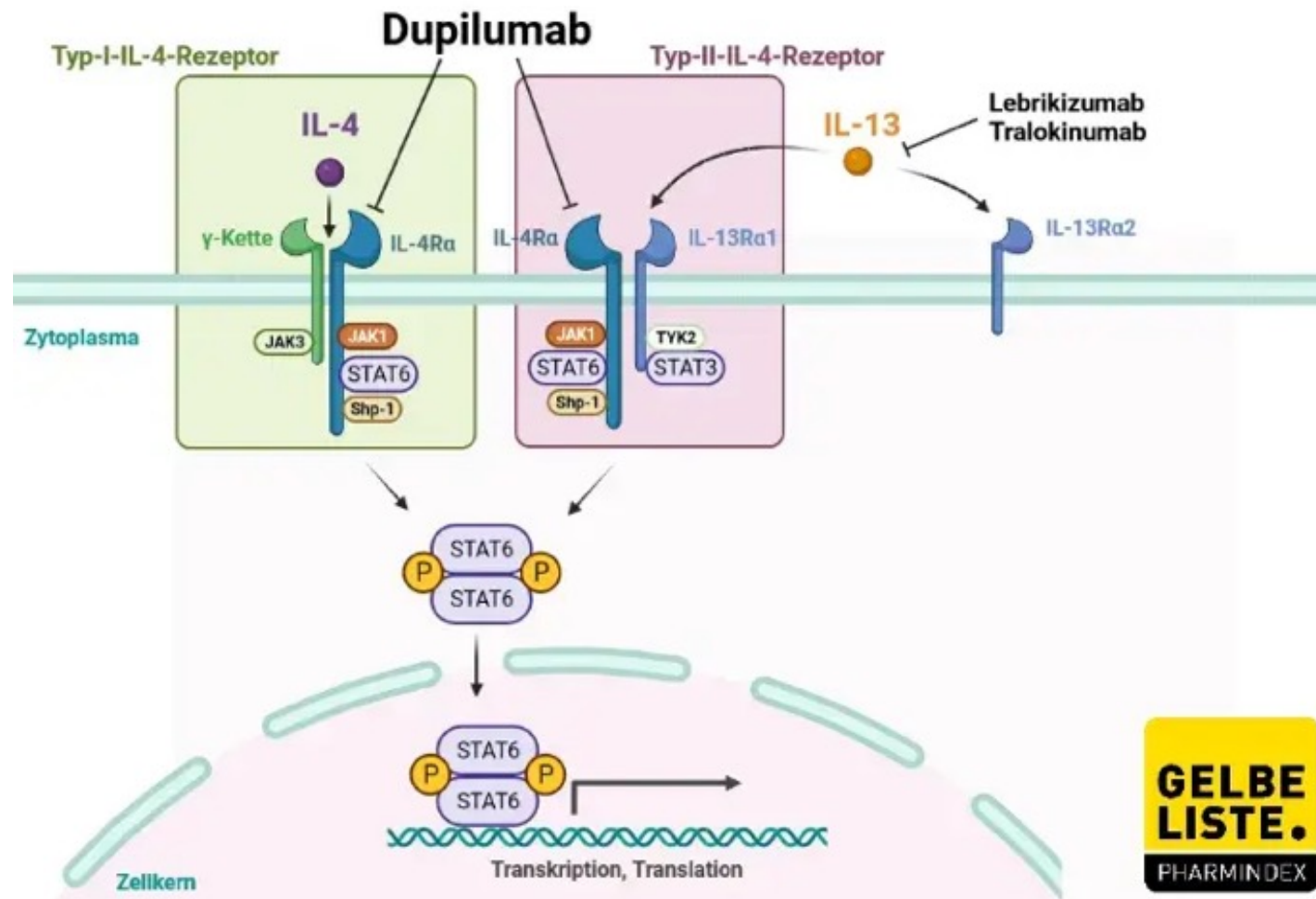
an allergic inflammatory condition of the esophagus that involves eosinophils, a type of white blood cell. In healthy individuals, the esophagus is typically devoid of eosinophils. In EoE, eosinophils migrate to the esophagus in large numbers. When a trigger food is eaten, the eosinophils contribute to tissue damage and inflammation. Symptoms include swallowing difficulty, food impaction, vomiting, and heartburn. Eosinophilic esophagitis was first described in children but also occurs in adults. The condition is not well understood, but food allergy may play a significant role. The treatment may consist of removal of known or suspected triggers and medication to suppress the immune response. In severe cases, it may be necessary to enlarge the esophagus with an endoscopy procedure.

While knowledge about EoE has been increasing rapidly, diagnosis of EoE can be challenging because the symptoms and histo-pathologic findings are not specific.

Typ-2-Entzündung: Was verbirgt sich dahinter? Die sogenannte **Typ-2-Entzündung** basiert auf einem Ungleichgewicht des Immunsystems ausgelöst durch Botenstoffe unseres Körpers, die bei Betroffenen im Überschuss vorhanden sind und verschiedene Krankheitssymptome hervorrufen.



Dupilumab ist ein monoklonaler Antikörper, der als Medikament zur Behandlung der atopischen Dermatitis (Neurodermitis), zur Add-on-Erhaltungstherapie bei schwerem Asthma sowie bei bestimmten Patienten mit schwerer Entzündung der Nasenwege und Nebenhöhlen (Rhinosinusitis) in Verbindung mit Nasenpolypen. Die Anwendung erfolgt durch subkutane Injektion. Dupilumab wirkt, indem es die α -Kette des Interleukin-4 Rezeptors (IL-4Ra, CD124) und damit zwei zentrale Zytokine der Th2-Immunantwort (**IL-4**, **IL-13**) blockiert. In zwei Phase-3-Studien hatte es 2016 vielversprechende Ergebnisse gezeigt.

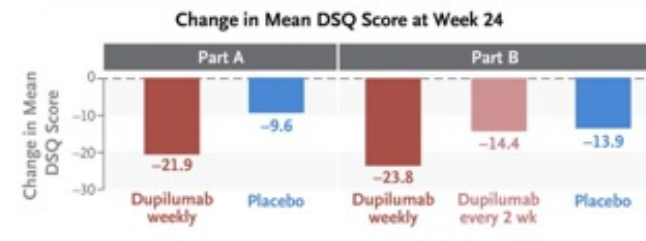
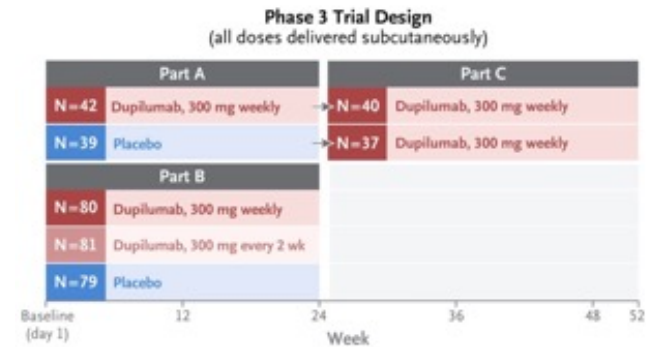


Dupilumab in Adults and Adolescents with Eosinophilic Esophagitis

Dupilumab, a fully human monoclonal antibody, blocks interleukin-4 and interleukin-13 signaling, which have key roles in **eosinophilic esophagitis**. We conducted a three-part, phase 3 trial in which patients 12 years of age or older underwent randomization in a 1:1 ratio to receive subcutaneous dupilumab at a weekly dose of 300 mg or placebo (Part A) or in a 1:1:1 ratio to receive 300 mg of dupilumab either weekly or every 2 weeks or weekly placebo (Part B) up to week 24. Eligible patients who completed Part A or Part B continued the trial in Part C, in which those who completed Part A received dupilumab at a weekly dose of 300 mg up to week 52 (the Part A–C group); Part C that included the eligible patients from Part B is ongoing. The two primary end points at week 24 were histologic remission (≤ 6 eosinophils per high-power field) and the change from baseline in the Dysphagia Symptom Questionnaire (DSQ) score (range, 0 to 84, with higher values indicating more frequent or more severe dysphagia).

LIMITATIONS AND REMAINING QUESTIONS

- The placebo-controlled treatment period, at 24 weeks, is relatively short given that eosinophilic esophagitis is a chronic, progressive disease.
- A high percentage of patients were White, which may limit generalizability of the results; however, the trial population was representative of the overall population with eosinophilic esophagitis.



Incidence of Adverse Events at Week 24

Adverse Event	Part A		Part B		
	Dupilumab, weekly (N=42)	Placebo (N=39)	Dupilumab, weekly (N=80)	Dupilumab, every 2 wk (N=81)	Placebo (N=78)
no. of patients (%)					
Death	0	0	0	0	0
Any adverse event	36 (86)	32 (82)	67 (84)	63 (78)	55 (71)
Serious adverse event	2 (5)	0	5 (6)	1 (1)	1 (1)

CONCLUSIONS

Among adults and adolescents with eosinophilic esophagitis, weekly dupilumab was associated with histologic improvement and reductions in symptoms.

Patients

Eligible patients were at least 12 years of age and had a documented diagnosis of eosinophilic esophagitis by endoscopic biopsy (peak eosinophil count, ≥ 15 per high-power field) despite 8 weeks of high-dose PPI therapy. All the patients had a score of 10 or greater on the Dysphagia Symptom Questionnaire (DSQ) at baseline (scores range from 0 to 84, with higher scores indicating more frequent or more severe dysphagia). Inclusion and exclusion criteria were identical in Parts A and B.

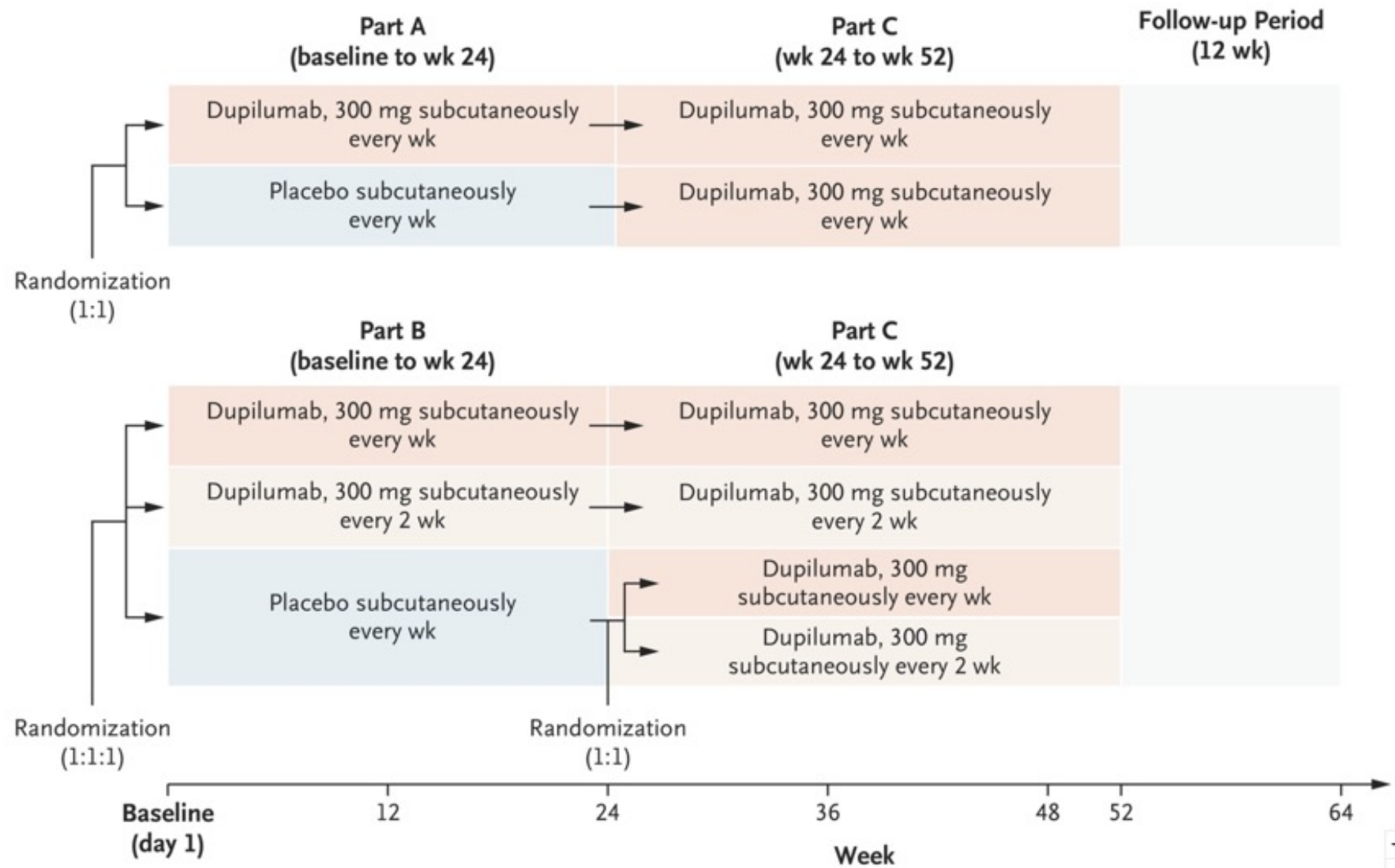
Interventions and Procedures

Randomization was stratified according to age group (≥ 12 to < 18 years and ≥ 18 years) and current use of PPIs. In Part A, patients were randomly assigned in a 1:1 ratio to receive subcutaneous dupilumab at a weekly dose of 300 mg or matching placebo up to week 24. In Part C, the patients in the Part A–C group received dupilumab at a weekly dose of 300 mg for an additional 28 weeks (up to week 52). In Part B, the patients were randomly assigned in a 1:1:1 ratio to receive 300 mg of dupilumab either weekly or every 2 weeks or weekly placebo up to week 24. Patients receiving dupilumab every 2 weeks also received placebo every 2 weeks, alternating with dupilumab, for regimen-blinding purposes. In Part C, the patients in the Part B–C group who had received dupilumab in Part B followed the same regimen in Part C, whereas those who received placebo in Part B were randomly assigned in a 1:1 ratio to receive 300 mg of dupilumab either weekly or every 2 weeks for an additional 28 weeks in Part C.

End Points

In Parts A and B, the two primary end points at week 24 were histologic remission (defined as a peak esophageal intraepithelial eosinophil count of ≤ 6 per high-power field) and the absolute change from baseline in the DSQ score. The DSQ scores were collected by means of a daily electronic diary assessing the frequency and severity of dysphagia; the scores were calculated over a 14-day period.

Phase 3 Trial Design.



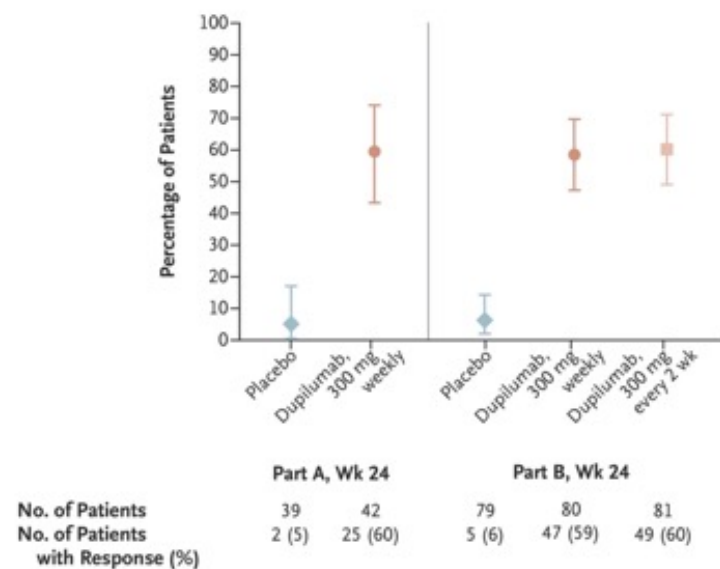
Selected Demographic and Clinical Characteristics of the Patients at Baseline (Full Analysis Set).

Characteristic	Part A			Part B			
	Dupilumab, 300 mg weekly (N=42)	Placebo (N=39)	Total (N=81)	Dupilumab, 300 mg weekly (N=80)	Dupilumab, 300 mg every 2 wk (N=81)	Placebo (N=79)	Total (N=240)
Age — yr	33.9±15.53	28.8±12.53	31.5±14.31	28.7±13.72	27.8±13.21	27.9±12.56	28.1±13.12
Female sex — no. (%)	14 (33)	18 (46)	32 (40)	30 (38)	36 (44)	21 (27)	87 (36)
Duration of eosinophilic esophagitis — yr†	5.23±4.18	4.77±4.55	5.01±4.34	5.89±4.66	5.92±5.18	4.88±4.48	5.57±4.79
Previous use of topical glucocorticoids for eosinophilic esophagitis — no. (%)	29 (69)	31 (79)	60 (74)	55 (69)	65 (80)	56 (71)	176 (73)
Refractory to previous therapy — no. (% of patients with previous use)	23 (79)	21 (68)	44 (73)	32 (58)	38 (58)	34 (61)	104 (59)
Inadequate response to or unacceptable side effects from previous therapy or current contraindication — no. (%)‡	—	—	—	38 (48)	41 (51)	39 (49)	118 (49)
History of esophageal dilation — no. (%)	18 (43)	17 (44)	35 (43)	26 (32)	26 (32)	33 (42)	85 (35)
Food elimination diet at screening — no. (%)	17 (40)	16 (41)	33 (41)	31 (39)	29 (36)	29 (37)	89 (37)
Presence of concurrent type 2 inflammatory disease — no. (%)	33 (79)	35 (90)	68 (84)	71 (89)	74 (91)	69 (87)	214 (89)
Allergic rhinitis	26 (62)	22 (56)	48 (59)	48 (60)	49 (60)	52 (66)	149 (62)
Food allergy	19 (45)	17 (44)	36 (44)	46 (58)	42 (52)	41 (52)	129 (54)
Asthma	10 (24)	15 (38)	25 (31)	32 (40)	31 (38)	27 (34)	90 (38)
Atopic dermatitis	6 (14)	9 (23)	15 (19)	12 (15)	17 (21)	19 (24)	48 (20)
DSQ score§	32.2±12.66	35.1±12.11	33.6±12.41	38.4±10.70	35.6±12.24	36.1±10.55	36.7±11.22
EREFS score¶	6.5±3.20	6.0±2.38	6.3±2.83	6.8±2.96	7.5±3.14	7.2±3.34	7.2±3.15
EoE-HSS grade score	1.26±0.41	1.32±0.47	1.29±0.44	1.31±0.39	1.25±0.37	1.23±0.40	1.26±0.39
EoE-HSS stage score	1.30±0.33	1.38±0.40	1.34±0.37	1.29±0.32	1.25±0.32	1.22±0.36	1.25±0.34
Peak eosinophil count per high-power field**	82.6±41.02	96.5±54.69	89.3±48.29	89.2±46.67	87.7±49.37	84.3±41.20	87.1±45.76
Median blood peripheral eosinophils (IQR) — IU/ml	430 (260–600)	450 (270–680)	440 (270–610)	420 (280–520)	380 (250–510)	430 (270–530)	400 (270–520)
Median IgE (IQR) — IU/ml	110 (51–463)	100 (47–294)	107 (50–306)	134 (48–302)	134 (47–362)	126 (52–416)	134 (48–330)

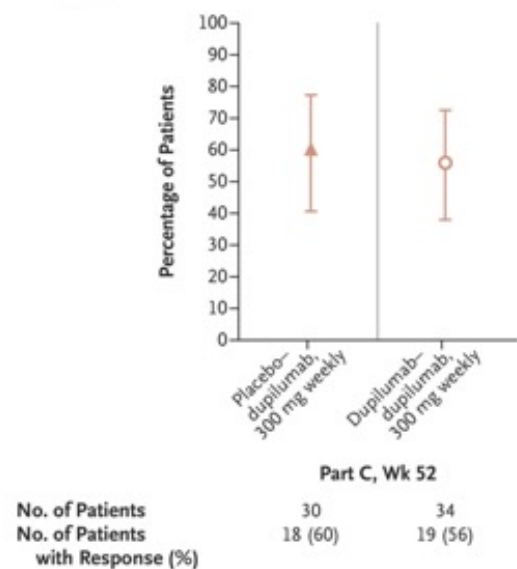
Dysphagia Symptom Questionnaire (DSQ), a patient-reported outcome (PRO) measure of dysphagia associated with EoE

Histologic Remission at Weeks 24 and 52.

A Histologic Remission at Wk 24 in Parts A and B

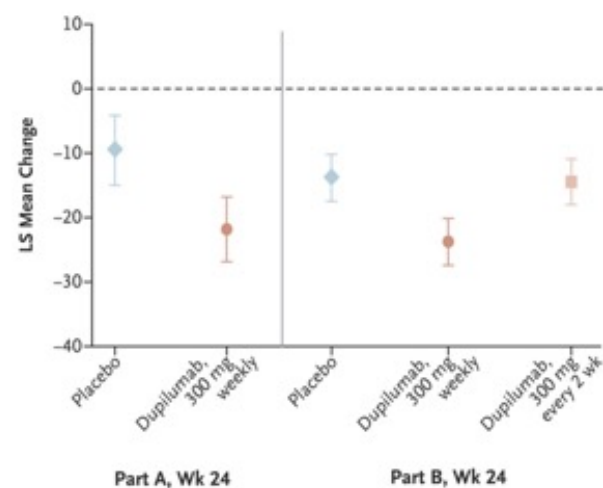


B Histologic Remission in the Part A–C Group Wk 52 in Part C

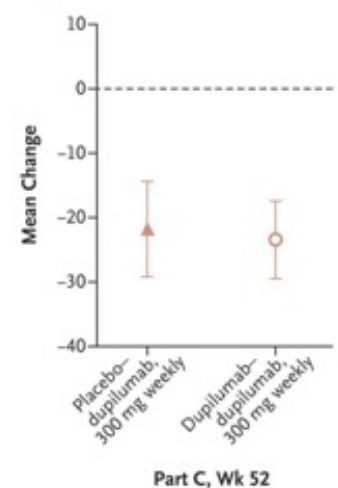


Change in DSQ Score at Weeks 24 and 52.

A Change from Baseline in DSQ Score in Parts A and B

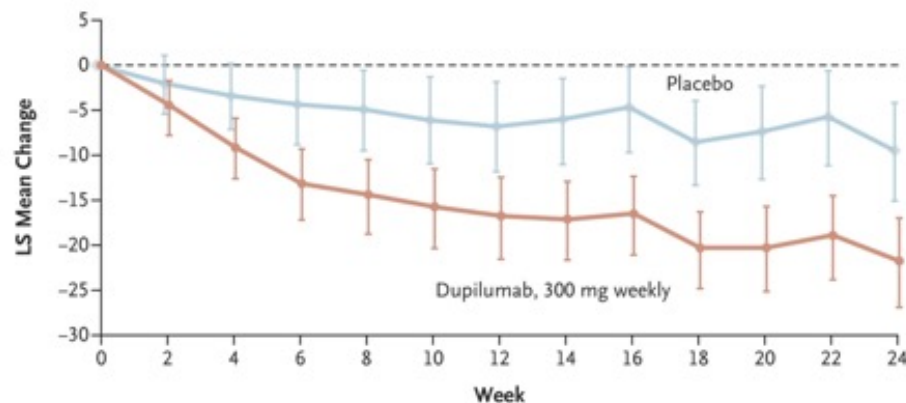


B Change from Baseline in DSQ Score in the Part A–C Group in Part C

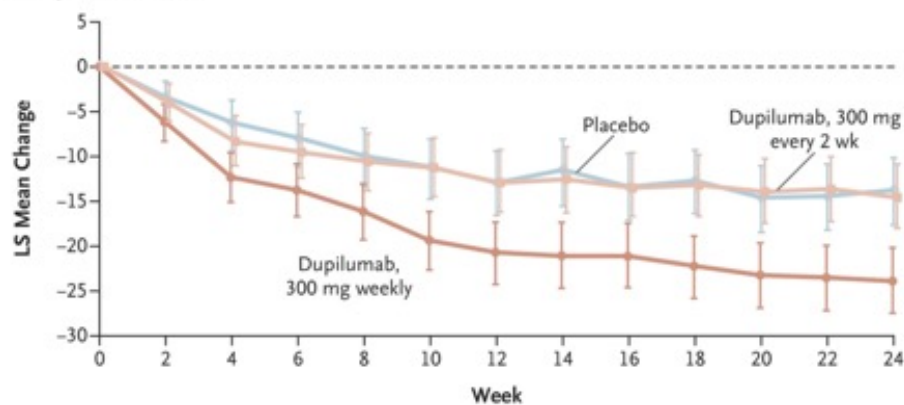


Change in DSQ Score over Time.

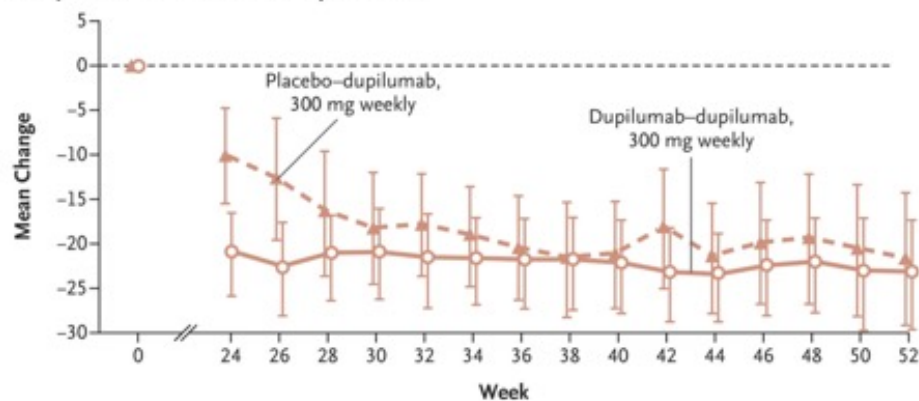
A Change from Baseline in DSQ Score in Part A



B Change from Baseline in DSQ Score in Part B



C Change from Baseline in DSQ Score in the Part A–C Group in Part C



Shown are the LS mean changes from baseline in the DSQ score over time in Part A (Panel A) and Part B (Panel B) of the trial and the mean changes from baseline in the DSQ score over time in the Part A–C group, which comprised the eligible patients from Part A who continued the trial in Part C (Panel C). In Part C, baseline was week 0 in Part A. Placebo–dupilumab indicates the patients who received placebo in Part A and weekly dupilumab in Part C, and dupilumab–dupilumab indicates the patients who received dupilumab weekly in Parts A and C. I bars indicate 95% confidence intervals, which were calculated with the use of Rubin's method for the LS mean changes in Parts A and B and with the use of normal approximation for the mean changes in Part C.

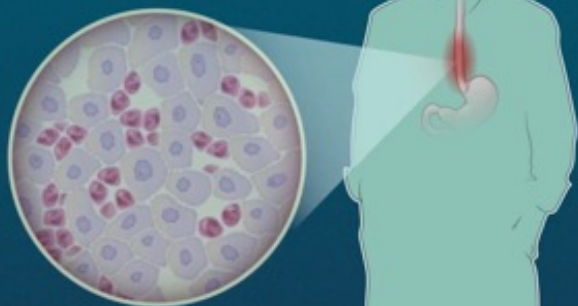
Incidence of Adverse Events during the Treatment Period (Safety Analysis Set).

Event	Part A		Part B			Part A–C Group in Part C	
	Dupilumab, 300 mg weekly (N=42)	Placebo (N=39)	Dupilumab, 300 mg weekly (N=80)	Dupilumab, 300 mg every 2 wk (N=81)	Placebo (N=78)	Dupilumab– dupilumab (N=40)	Placebo– dupilumab (N=37)
	<i>number of patients (percent)</i>						
Deaths	0	0	0	0	0	0	0
Adverse event	36 (86)	32 (82)	67 (84)	63 (78)	55 (71)	24 (60)	27 (73)
Serious adverse event†	2 (5)	0	5 (6)	1 (1)	1 (1)	0	1 (3)
Adverse event leading to dis- continuation†	1 (2)	0	2 (2)	2 (2)	2 (3)	0	2 (5)
Adverse event occurring in ≥10% of patients in any group‡							
Injection-site reaction	7 (17)	4 (10)	16 (20)	18 (22)	16 (21)	4 (10)	8 (22)
Injection-site erythema	3 (7)	5 (13)	8 (10)	18 (22)	9 (12)	4 (10)	5 (14)
Injection-site pain	4 (10)	3 (8)	7 (9)	10 (12)	4 (5)	2 (5)	3 (8)
Injection-site swelling	3 (7)	1 (3)	10 (12)	7 (9)	2 (3)	2 (5)	0
Nasopharyngitis	5 (12)	4 (10)	2 (2)	4 (5)	3 (4)	1 (2)	3 (8)
Headache	2 (5)	4 (10)	6 (8)	5 (6)	9 (12)	3 (8)	2 (5)
Acne	0	1 (3)	0	2 (2)	3 (4)	0	4 (11)
Rash	0	4 (10)	2 (2)	4 (5)	0	1 (2)	0

Serious adverse events occurred in 9 patients during the Part A or B treatment period (in 7 who received weekly dupilumab, 1 who received dupilumab every 2 weeks, and 1 who received placebo) and in 1 patient during the Part C treatment period who had received placebo in Part A and weekly dupilumab in Part C. No deaths occurred among the patients in Part A or Part B or among those in the Part A–C group in Part C.

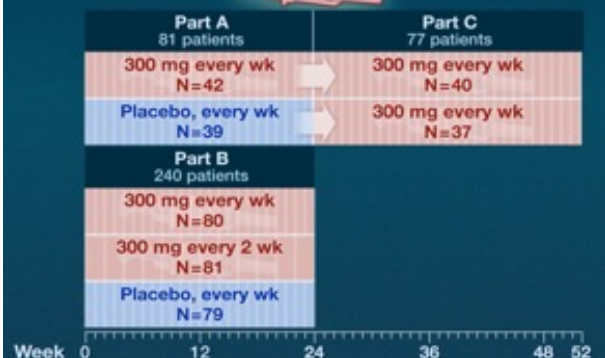
Eosinophilic Esophagitis (EoE)

Chronic, progressive, type 2 inflammatory disease



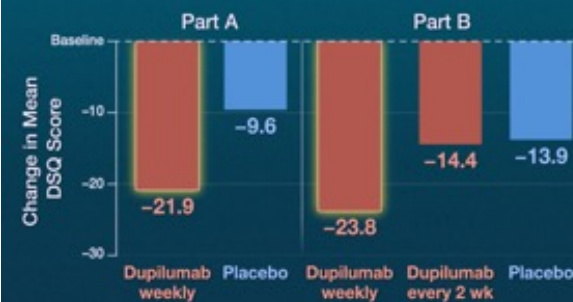
Trial Design

Subcutaneous Dupilumab



Primary Efficacy End Point

Change from Baseline in Mean DSQ Score at Week 24



Many patients do not respond to first-line treatments or have adverse events

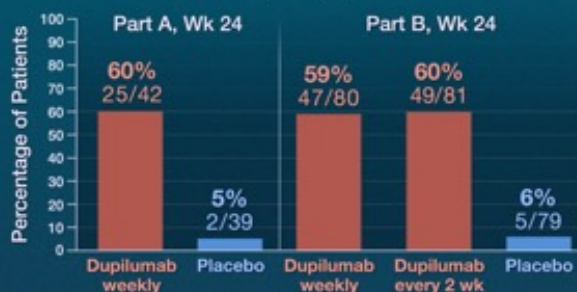


- Food elimination diets
- Proton-pump inhibitors
- Swallowed topical glucocorticoids

Primary Efficacy End Point

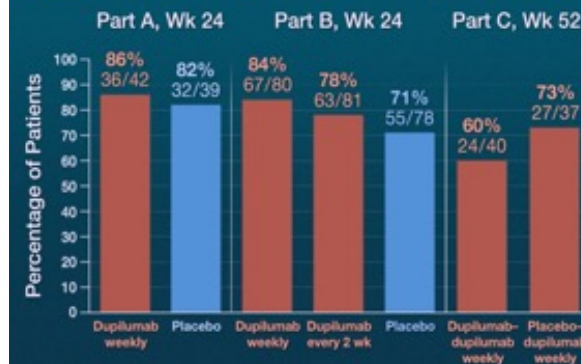
Histologic Remission

Peak esophageal intraepithelial eosinophil count of ≤ 6 per high-power field



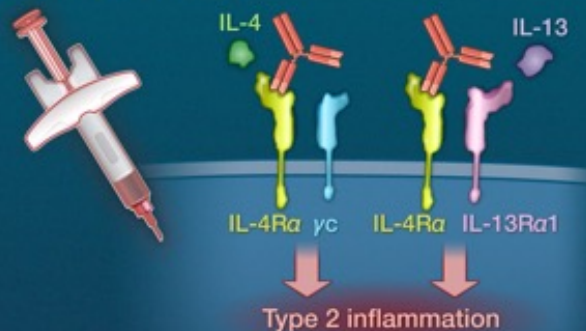
Adverse Events

Adverse Events during Treatment Period



Dupilumab

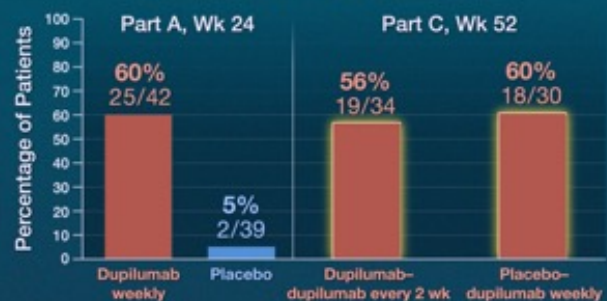
Monoclonal antibody



Primary Efficacy End Point

Histologic Remission

Peak esophageal intraepithelial eosinophil count of ≤ 6 per high-power field



Weekly subcutaneous dupilumab
Works but you need to squirt it every week

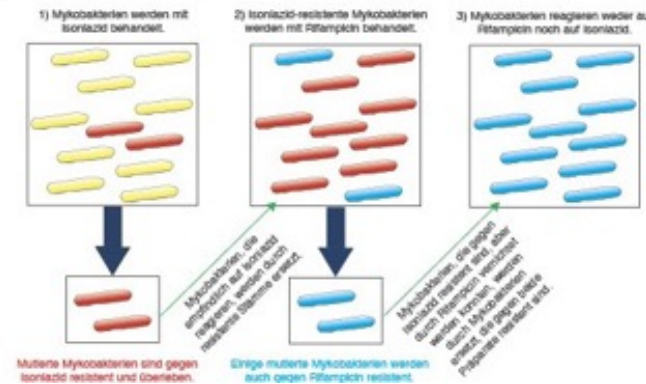


Was ist MDR-TB?

MDR-TB ist eine besondere Form der Tuberkulose und wird durch Mykobakterien verursacht, die gegen die wirksamsten Anti-TB-Medikamente, Isoniazid und Rifampicin, resistent sind.

Somit muss MDR-TB mit anderen Präparaten – so genannten Second-Line-Medikamenten – behandelt werden. Die Behandlung ist langwieriger, teurer und schwieriger. Wie andere Bakterien können sich auch Mykobakterien genetisch verändern (mutieren). Dadurch können sie eine natürliche Resistenz gegen Anti-TB-Präparate entwickeln. Eine Behandlung mit 3 oder 4 Präparaten kann verhindern, dass resistente Mykobakterien wachsen und „empfindliche“ Mykobakterien ersetzen, die durch die übliche TB-Behandlung vernichtet wurden.

Das Diagramm zeigt, wie sich MDR-TB entwickelt und gegen Isoniazid und Rifampicin resistent wird.



Wodurch wird MDR-TB verursacht?

MDR-TB ist immer ein Ergebnis menschlichen Versagens, beispielsweise wenn ein Patient seine Behandlung nicht vollständig zu Ende führt. **Die Hauptgründe für MDR-TB sind:** Verschreibung ungeeigneter Präparate, mangelhafte Qualität der Anti-TB-Medikamente, Behandlungsunterbrechung, Fehlen von nationalen TB-Bekämpfungsprogrammen und standardisierten Richtlinien sowie ineffiziente Beaufsichtigung durch Ärzte oder Behandlungsabbruch. Wird MDR-TB nicht erkannt, haben resistente Mykobakterien mehr Zeit, um auf andere Menschen übertragen zu werden und somit das Problem zu verschlimmern.

Rifampin-Resistant TB



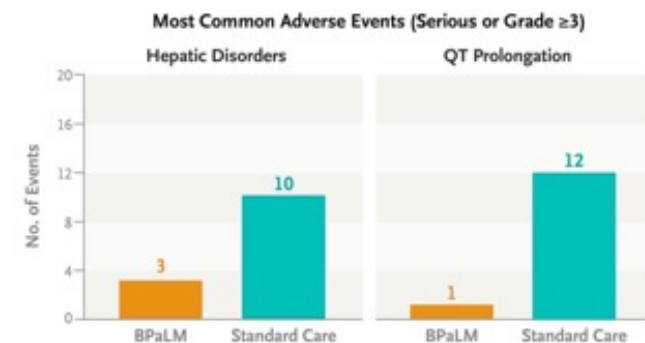
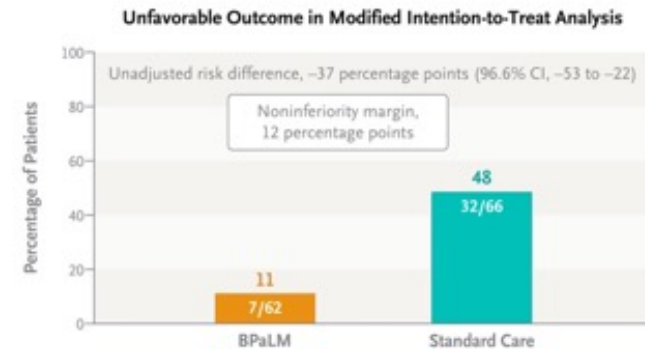
Recommended Treatments 9 to 20 Months



Up to 20 tablets daily

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

In patients with **rifampin-resistant tuberculosis**, all-oral treatment regimens that are more effective, shorter, and have a more acceptable side-effect profile than current regimens are needed. We conducted an open-label, phase 2–3, multicenter, randomized, controlled, **noninferiority trial** to evaluate the efficacy and safety of three 24-week, all-oral regimens for the treatment of rifampin-resistant tuberculosis. Patients in Belarus, South Africa, and Uzbekistan who were 15 years of age or older and had rifampin-resistant pulmonary tuberculosis were enrolled. In stage 2 of the trial, a 24-week regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (**BPaLM**) was compared with a 9-to-20-month standard-care regimen. The primary outcome was an unfavorable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at **72 weeks after randomization**. The noninferiority margin was 12 percentage points.



CONCLUSIONS

In patients with rifampin-resistant tuberculosis, a 24-week, all-oral BPaLM regimen was noninferior to the standard-care regimen with respect to unfavorable outcomes, and it had a better safety profile.

Patients

Patients 15 years of age or older who had rifampin-resistant pulmonary tuberculosis were enrolled at seven sites in Belarus, South Africa, and Uzbekistan. The major inclusion criterion was *Mycobacterium tuberculosis* infection (as confirmed by a positive sputum smear) with resistance to rifampin. Patients were included irrespective of fluoroquinolone resistance, human immunodeficiency virus (HIV) status, or CD4 count. Patients were excluded if they were pregnant or if they had an alanine aminotransferase level or an aspartate aminotransferase level higher than 3 times the upper limit of the normal range, a corrected QT interval calculated with the use of Fridericia's formula (QTcF) greater than 450 msec, structural heart disease, or suspected resistance to bedaquiline, pretomanid, or linezolid. All the patients provided written informed consent.

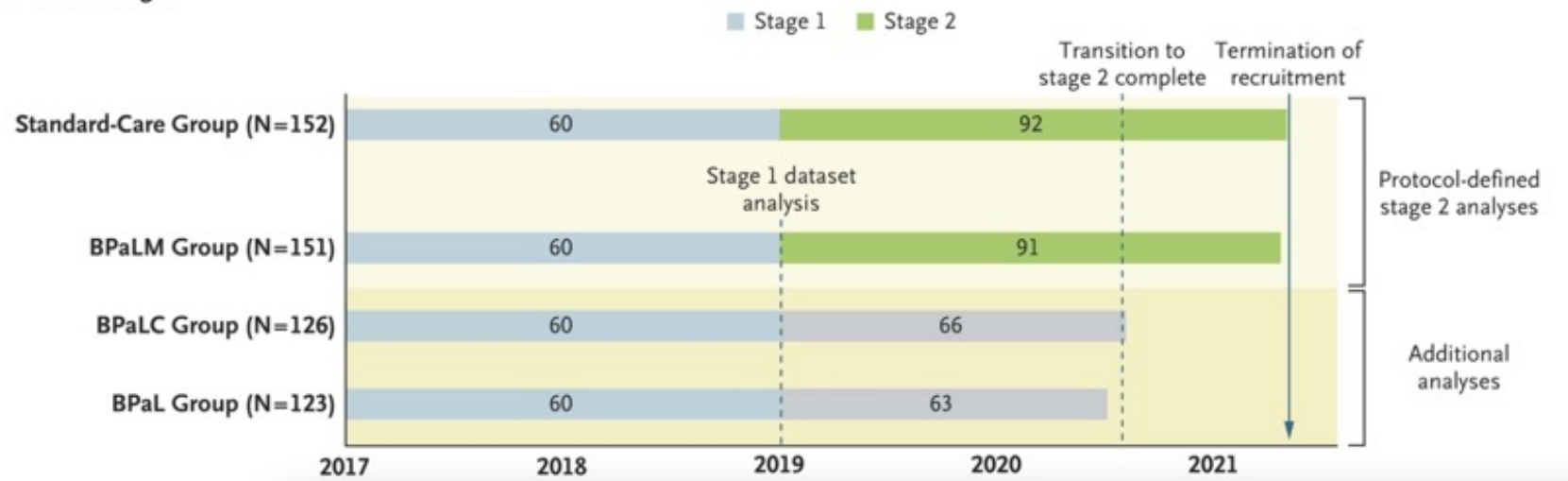
Treatment

In stage 1 of the trial, enrolled patients were randomly assigned to the locally accepted standard-care treatment or to one of three investigational regimens. The standard-care regimen consisted of locally accepted treatment regimens. These regimens were closely aligned with the World Health Organization (WHO) guidelines for treatment of drug-resistant tuberculosis, and the agents (some oral and some intravenous) were administered at least 6 days per week with food and under observation.

All the investigational agents were administered orally, with food and under observation, 7 days per week. The BPaL regimen consisted of the following: bedaquiline at a dose of 400 mg daily for 2 weeks, followed by 200 mg three times per week for 22 weeks; pretomanid at a dose of 200 mg daily for 24 weeks; and linezolid at a dose of 600 mg daily for 16 weeks, followed by 300 mg daily for 8 weeks. The BPaLM regimen included BPaL plus moxifloxacin at a dose of 400 mg daily for 24 weeks, and the BPaLC regimen included BPaL plus clofazimine at a dose of 100 mg daily (or 50 mg if the patient weighed <30 kg) for 24 weeks. In stage 2 of the trial, patients were enrolled either into the standard-care group or into one of two investigational groups.

Panel B shows the trial design. The trial was designed as a phase 2–3 clinical trial with a seamless transition from phase 2b to phase 3. Stage 1 included 240 patients with 60 patients in each group. A planned analysis involving the investigational groups only was then conducted to select groups for evaluation in stage 2. Evaluable patients included those who were enrolled in stage 1 and subsequently were included in the groups in stage 2. The first patient underwent randomization and the first visit occurred in January 2017, and stage 1 recruitment was completed in mid-2019. All three investigational groups met the eligibility criteria for progression to stage 2, but the trial steering committee elected to proceed with the BPaLM group only. Recruitment continued through the transition period across all four groups. Patients in all the groups underwent follow-up in accordance with the protocol for a minimum of 72 weeks after randomization. BPaL denotes bedaquiline, pretomanid, and linezolid; BPaLC bedaquiline, pretomanid, linezolid, and clofazimine; and BPaLM bedaquiline, pretomanid, linezolid, and moxifloxacin.

B Trial Design



Characteristic	Standard-Care Group	BPaLM Group	BPaLC Group	BPaL Group
Intention-to-treat population				
No. of patients	152	151	126	123
Geographic distribution — no. (%)				
Belarus	29 (19.1)	28 (18.5)	21 (16.7)	21 (17.1)
South Africa	54 (35.5)	56 (37.1)	48 (38.1)	47 (38.2)
Uzbekistan	69 (45.4)	67 (44.4)	57 (45.2)	55 (44.7)
Median age (range) — yr	37 (18–71)	35 (17–71)	32 (15–67)	35 (15–72)
Female sex — no. (%)	56 (36.8)	66 (43.7)	42 (33.3)	58 (47.2)
Median BMI (IQR)†	19.9 (17.3–22.8)	19.8 (17.7–22.7)	19.5 (17.7–22.2)	20.0 (18.1–22.4)
HIV-positive status — no. (%)	41 (27.0)	38 (25.2)	33 (26.2)	41 (33.3)
Median CD4 cell count (IQR) in HIV-infected patients — cells/mm³‡	250 (132–460)	330 (209–547)	297 (114–481)	326 (153–550)
Smear positivity — no. (%)	98 (64.5)	91 (60.3)	84 (66.7)	77 (63)
Cavitation on chest radiography present — no. (%)	95 (62.5)	80 (53.0)	79 (62.7)	74 (60.2)
Fluoroquinolone-resistant tuberculosis — no./total no. (%)	32/131 (24.4)	32/134 (23.9)	22/118 (18.6)	25/104 (24.0)
QTcF interval — msec§	401±19	398±19	395±19	398±19
Median ALT level (IQR) — IU/liter¶	20 (15–28)	19 (14–28)	17 (14–26)	20 (14–31)
Modified intention-to-treat population with 72 wk of follow-up				
No. of patients	66	62	64	60
Geographic distribution — no. (%)				
Belarus	12 (18)	10 (16)	10 (16)	11 (18)
South Africa	18 (27)	16 (26)	19 (30)	16 (27)
Uzbekistan	36 (55)	36 (58)	35 (55)	33 (55)
Median age (range) — yr	36 (19–71)	34 (18–61)	29 (19–63)	34 (18–62)
Female sex — no. (%)	33 (50)	26 (42)	24 (38)	28 (47)
Median BMI (IQR)	19.2 (17.3–22.0)	19.8 (18.1–22.1)	18.8 (17.4–22.0)	20.5 (18.2–22.8)
HIV-positive status — no. (%)	15 (22.7)	14 (23)	14 (22)	14 (23)
Median CD4 cell count (IQR) — cells/mm³	317 (154–383)	268 (182–364)	394 (112–511)	283 (153–424)
Smear positivity — no. (%)	50 (76)	40 (65)	43 (67)	45 (75)
Cavitation on chest radiography present — no. (%)	47 (71)	33 (53)	39 (61)	41 (68)
Fluoroquinolone-resistant tuberculosis — no./total no. (%)	18/65 (28)	17/60 (28)	16/62 (26)	19/56 (34)
QTcF interval — msec	398±18	396±18	393±20	398±18
Median ALT level (IQR) — IU/liter**	20 (15–27)	18 (14–27)	18 (15–27)	19 (14–27)

Primary Efficacy Analysis at 72 Weeks (stage 2).

Variable	Intention-to-Treat Population		Modified Intention-to-Treat Population		Per-Protocol Population*	
	Standard-Care Group (N=73)	BPaLM Group (N=72)	Standard-Care Group (N=66)	BPaLM Group (N=62)	Standard-Care Group (N=33)	BPaLM Group (N=57)
Favorable outcome — no. (%)	34 (47)	55 (76)	34 (52)	55 (89)	29 (88)	55 (96)
Primary outcome: unfavorable status — no. (%)	39 (53)	17 (24)	32 (48)	7 (11)	4 (12)	2 (4)
Death — no. (%)	2 (3)	0	2 (3)	0	2 (6)	0
Early discontinuation — no. (%)	35 (48)	15 (21)	28 (42)	5 (8)	—	—
Adherence issues — no./total no. (%)	3/35 (9)	0	3/28 (11)	0	—	—
Adverse event — no./total no. (%)	17/35 (49)	5/15 (33)	17/28 (61)	5/5 (100)	—	—
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	10/15 (67)	0	0	—	—
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0	6/28 (21)	0	—	—
Other reason — no./total no. (%)†	2/35 (6)	0	2/28 (7)	0	—	—
Treatment failure — no.	0	0	0	0	0	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	2 (3)	2 (3)	2 (3)	2 (6)	2 (4)
Recurrence — no.	0	0	0	0	0	0
Risk difference for the primary outcome — percentage points (96.6% CI)‡	—	-30 (-46 to -14)	—	-37 (-53 to -22)	—	-9 (-22 to 4)

BPaLM beats standard care (surely no worse)

Outcomes at 72 Weeks in the Standard-Care, BPaLC, and BPaL Groups.

Variable	Intention-to-Treat Population			Modified Intention-to-Treat Population			Per-Protocol Population		
	Standard-Care Group (N=73)	BPaLC Group (N=72)	BPaL Group (N=70)	Standard-Care Group (N=66)	BPaLC Group (N=64)	BPaL Group (N=60)	Standard-Care Group (N=33)	BPaLC Group (N=58)	BPaL Group (N=52)
Favorable outcome — no. (%)	34 (47)	52 (72)	46 (66)	34 (52)	52 (81)	46 (77)	29 (88)	52 (90)	46 (88)
Primary outcome: unfavorable status — no. (%)	39 (53)	20 (28)	24 (34)	32 (48)	12 (19)	14 (23)	4 (12)	6 (10)	6 (12)
Death — no. (%)	2 (3)	1 (1)	0	2 (3)	1 (2)	0	2 (6)	1 (2)	0
Early discontinuation — no. (%)	35 (48)	14 (19)	18 (26)	28 (42)	6 (9)	8 (13)	—	—	—
Adherence issues — no./total no. (%)	3/35 (9)	2/14 (14)	2/18 (11)	3/28 (11)	2/6 (33)	2/8 (25)	—	—	—
Adverse event — no./total no. (%)	17/35 (49)	4/14 (29)	5/18 (28)	17/28 (25)	4/6 (67)	5/8 (62)	—	—	—
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	8/14 (57)	10/18 (6)	0	0	1/8 (12)	—	—	—
Did not receive at least one dose of trial medication — no./total no. (%)	0	0	1/18 (6)	—	—	—	—	—	—
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0	0	6/28 (21)	0	0	—	—	—
Other reason — no./total no. (%)†	2/35 (6)	0	0	2/28 (7)	0	0	—	—	—
Treatment failure — no. (%)	0	1 (1)	0	0	1 (2)	0	0	1 (2)	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	3 (4)	3 (4)	2 (3)	3 (5)	3 (5)	2 (6)	3 (5)	3 (6)
Recurrence — no. (%)	0	1 (1)	3 (4)	0	1 (2)	3 (5)	0	1 (2)	3 (6)
Risk difference for the primary outcome — percentage points (95% CI)	—	-26 (-41 to -10)	-19 (-36 to -2)	—	-30 (-45 to -14)	-25 (-41 to -9)	—	-2 (-15 to 12)	-1 (-15 to 14)

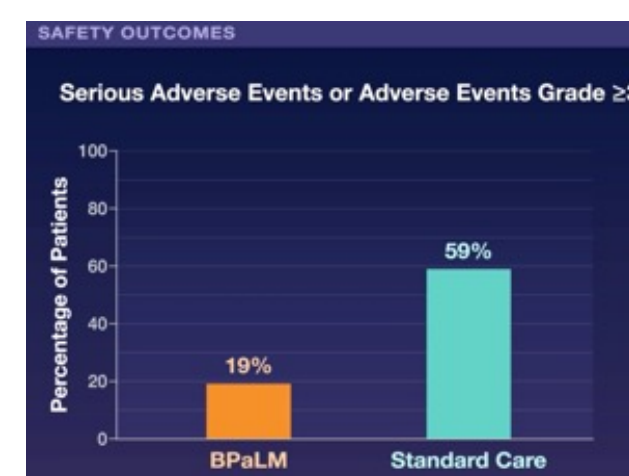
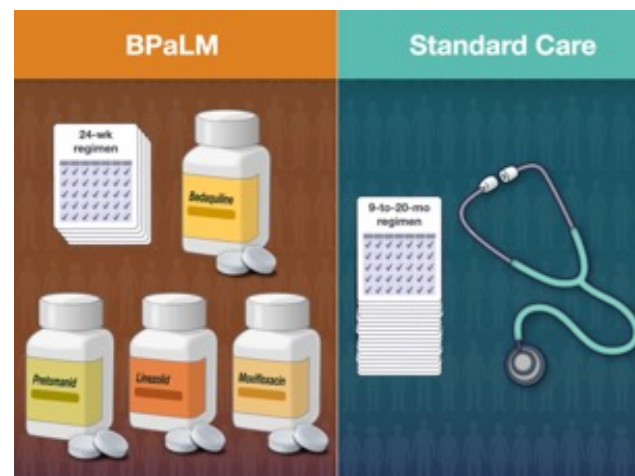
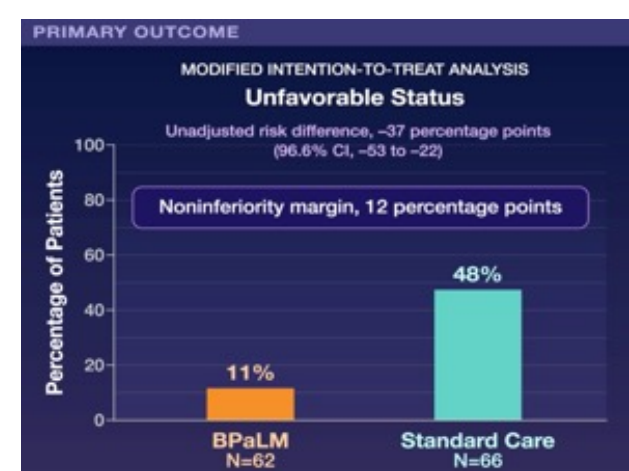
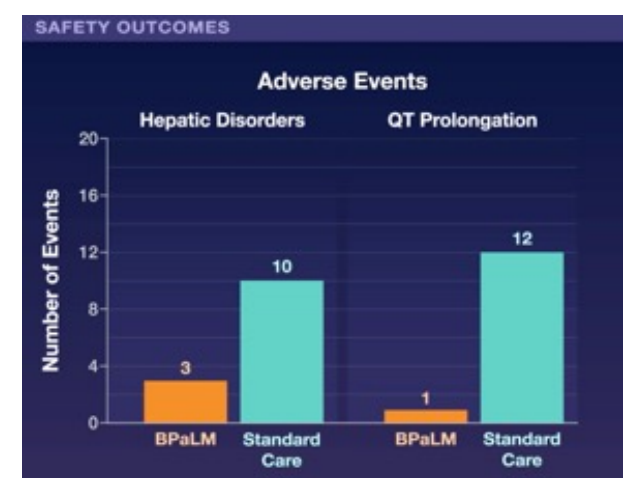
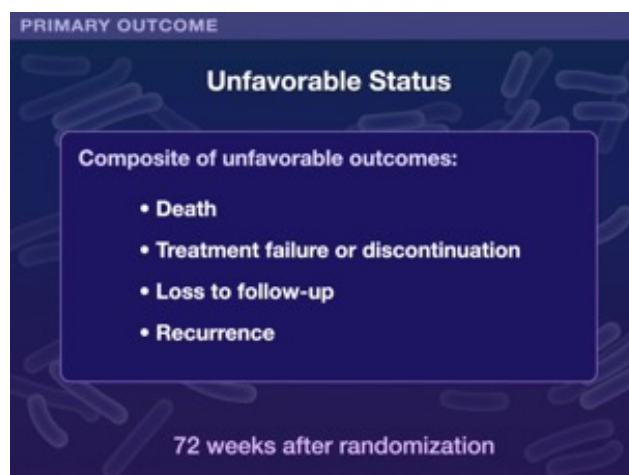
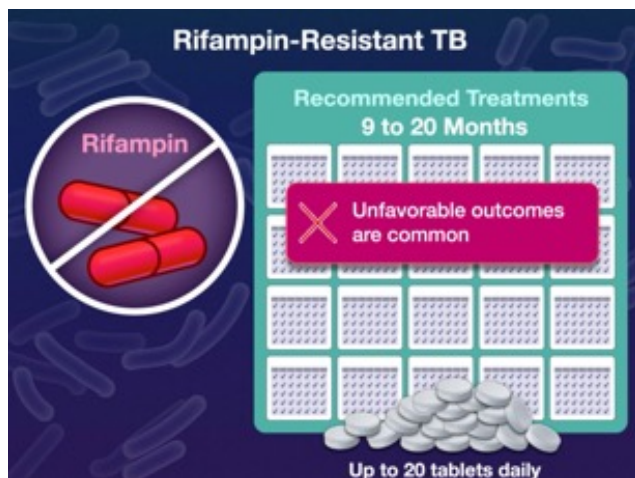
BPaLM beats standard care (surely no worse)

Safety Outcomes (As-Treated Population).

By 72 weeks, the most frequently observed serious or grade 3 or higher adverse events were **hepatic disorders**. None of the patients in any of the groups met the Hy's law criteria for drug-induced liver injury. **QTcF prolongation**, the second most frequent serious or grade 3 or higher adverse event, affected 14 patients: 10 of 73 patients in the standard-care group (14%), 1 of 72 patients in the BPaLM group (1%), 3 of 72 patients in the BPaLC group (4%), and none of the patients in the BPaL group. QTcF prolongation for more than 500 msec led to early discontinuation of treatment in 6 patients in the standard-care group and in 1 patient in any of the investigational groups (the BPaLC group). Peripheral neuropathy (any grade) was seen in 28 of 150 patients in the standard-care group (19%; a total of 33 events), in 14 of 151 patients in the BPaLM group (9%; a total of 15 events), in 10 of 126 patients in the BPaLC group (8%; a total of 10 events), and in 16 of 122 patients in the BPaL group (13%; a total of 19 events).

Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury (not Hepatobiliary injury) with jaundice.

Variable	Standard-Care Group	BPaLM Group	BPaLC Group	BPaL Group
QTcF interval at 24 wk				
No. of patients with data†	71	98	92	92
QTcF interval at 24 wk — msec	441.8±18.0	423.5±18.5	435.7±17.6	423.1±18.5
Mean difference (CI) — msec§	—	-18.1 (-23.4 to -12.8)	-5.4 (-10.3 to -0.6)	-20.0 (-25.1 to -14.9)
Serious adverse event or grade ≥3 adverse event within 108 wk after randomization				
Patients with at least 1 event — no./total no. (%)	26/43 (60)	10/40 (25)	18/43 (42)	11/43 (26)
No. of events	48	11	22	21
Risk difference — percentage points (CI)§	—	-36 (-57 to -14)	-19 (-39 to 2)	-35 (-54 to -15)
Serious adverse event or grade ≥3 adverse events during treatment and up to 30 days after treatment end date				
Patients with at least 1 event — no./total no. (%)	25/43 (58)	7/40 (18)	11/43 (26)	10/43 (23)
No. of events	46	7	14	12
Risk difference — percentage points (CI)§	—	-41 (-61 to -20)	-33 (-52 to -13)	-35 (-54 to -16)
Serious adverse event or grade ≥3 adverse events within 72 wk after randomization				
Patients with at least 1 event — no./total no. (%)	43/73 (59)	14/72 (19)	23/72 (32)	15/69 (22)
No. of events	69	16	32	24
Risk difference — percentage points (CI)§	—	-40 (-55 to -24)	-27 (-43 to -11)	-37 (-52 to -22)
Hepatic disorder, grouped				
No. of events	10	3	5	2
Patients with events — no./total no. (%)	8/73 (11)	3/72 (4)	3/72 (4)	2/69 (3)
QTcF prolongation¶				
No. of events	12	1	3	0
Patients with events — no./total no. (%)	10/73 (14)	1/72 (1)	3/72 (4)	0
Creatinine renal clearance decreased				
No. of events	7	1	0	2
Patients with events — no./total no. (%)	5/73 (7)	1/72 (1)	0	2/69 (3)
Anemia				
No. of events	6	2	0	1
Patients with events — no./total no. (%)	6/73 (8)	2/72 (3)	0	1/69 (1)
Neutropenia				
No. of events	2	3	0	0
Patients with events — no./total no. (%)	2/73 (3)	3/72 (4)	0	0
Lipase level increased or pancreatitis				
No. of events	1	2	2	2
Patients with events — no./total no. (%)	1/73 (1)	2/72 (3)	2/72 (3)	2/69 (3)
Acute kidney injury				
No. of events	1	1	0	1
Patients with events — no./total no. (%)	1/73 (1)	1/72 (1)	0	1/69 (1)
Hemoptysis‡				
No. of events	2	0	1	0
Patients with events — no./total no. (%)	1/73 (1)	0	1/72 (1)	0
Vomiting				
No. of events	2	0	0	0
Patients with events — no./total no. (%)	2/73 (3)	0	0	0
Lymphocyte count decreased				
No. of events	0	1	1	1
Patients with events — no./total no. (%)	0	1/72 (1)	1/72 (1)	1/69 (1)
Pneumonia				
No. of events	1	0	2	1
Patients with events — no./total no. (%)	1/73 (1)	0	2/72 (3)	1/69 (1)
Other‡				
No. of events	25	2	18	14
Patients with events — no./total no. (%)	23/73 (32)	2/72 (3)	18/72 (25)	12/69 (17)



LIMITATIONS AND REMAINING QUESTIONS

- The performance of standard-care treatment was affected by early treatment discontinuations. Although more than half the discontinuations were due to adverse events, the rest could have been subject to performance bias given the open-label design of the trial.
- The standard-care regimen differed over time and according to treatment site.

Schwerer kombinierter Immundefekt, **kurz SCID**, ist ein **Sammelbegriff** für angeborene Immundefekte, bei denen die T-Lymphozyten defekt sind oder ganz fehlen. Dadurch sind sowohl die zellvermittelte Immunabwehr als auch häufig die humorale Abwehr ungenügend ausgebildet. SCID ist eine seltene Erkrankung, die Prävalenz in Deutschland wird auf **1:60.000 bei Neugeborenen** geschätzt. SCID wird durch Genmutationen ausgelöst. Es gibt mehrere SCID-Formen, bei einigen sind die genauen genetischen Ursachen noch nicht bekannt. Vorherrschend sind Defekte folgender Gene:

- Zytokinrezeptor-Gene
- Antigenrezeptor-Gene
- ADA-Gene (Adenosin-Desaminase-Gene)

Enzym spielt eine Rolle beim Abbau von Purinen, die z.B. in der DNA vorkommen. Werden Purine, insbesondere Adenosin, nicht abgebaut, reichern sie sich im Körper an und werden in andere Stoffe umgebaut. Dabei entsteht vor allem Desoxyadenosintriphosphat (dATP), welches wiederum das Enzym Ribonukleotid-Reduktase hemmt. Die Ribonukleotid-Reduktase ist wichtig für die Synthese der DNA in Lymphozyten. Wenn nicht genug DNA gebildet werden kann, kommt es zu einer Proliferationsstörung der Zellen. Außerdem hemmt die Anreicherung von Adenosin die S-Adenosyl-Homocystein-Hydrolase, die für die DNA-Methylierung zuständig ist. Weiterhin induziert die Akkumulation der Metaboliten direkt die Apoptose.

Jesse Gelsinger war die erste öffentlich identifizierte Person, die in einer klinischen Studie zur Gentherapie gestorben ist. Verstorben: 17. September 1999, University of Pennsylvania, Philadelphia,



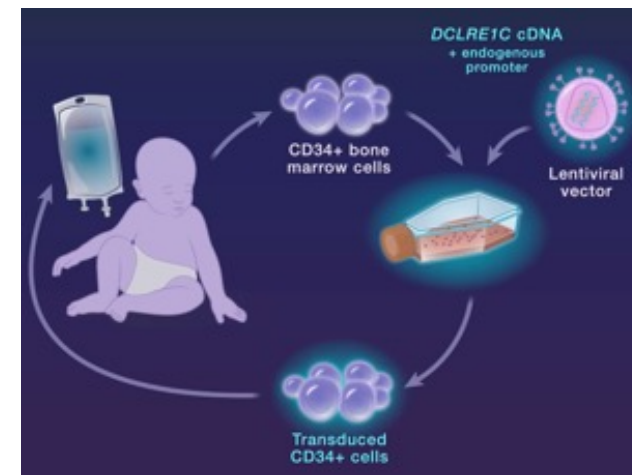
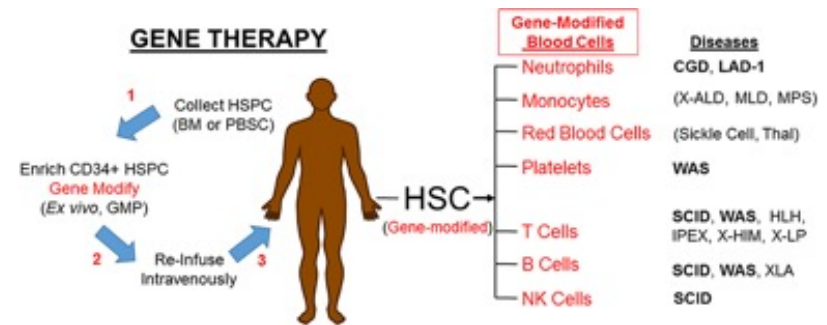
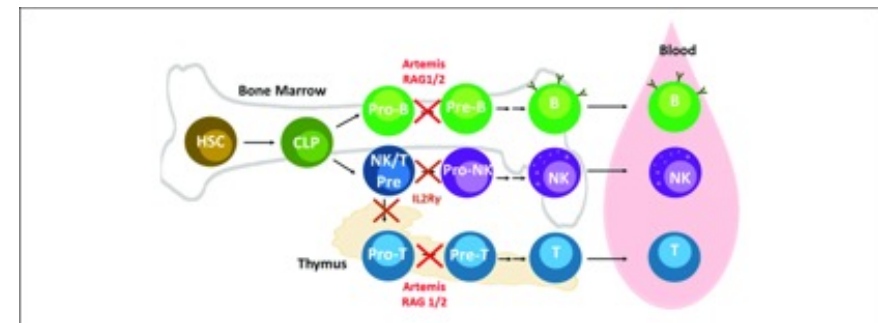
Jesse had a rare metabolic disorder called ornithine transcarbamylase deficiency syndrome, or OTCD, in which ammonia builds up to lethal levels in the blood. Babies born with OTCD usually fall into comas soon after birth and suffer brain damage.

Mutations in the gene for **Artemis (DCLRE1C)** cause a **rare form of autosomal recessive radiosensitive SCID** which results in a T-B-NK+ phenotype. This type of SCID was originally described in Athabascan-speaking native Americans.

Similar to other types of SCID, presentation occurs in infancy with lymphopenia, FTT, diarrhea, candidiasis, and Pneumocystis jiroveci pneumonia. Patients with an Omenn syndrome phenotype have also been described. T and B cell numbers are markedly decreased but NK cell numbers are normal. Patients have an increased risk of developing lymphomas.

Artemis is protein in the pathway that mediates repair of **DNA double-strand breaks (dsb)** by nonhomologous end-joining (NHEJ) – this process is required for T cell and B cell V(D)J recombination. Artemis interacts with DNA-PKcs and plays a role in opening of the DNA hairpin that is formed following double-stranded breaks introduced by RAG.

The diagnosis of Artemis deficiency is suggested by a T-B-NK+ SCID phenotype and radiosensitivity. The definitive diagnosis is made by sequencing of the DCLRE1C gene.



The T cell-negative (T-), B cell-negative (B-), natural killer cell-positive (NK+) SCID phenotype, which accounts for approximately one-quarter to one-half of all cases of SCID. Unless identified by newborn screening (NBS) or a positive family history, children with T-B-NK+ SCID present early in life with serious to life-threatening infections, failure to thrive, low to absent T and B cell numbers and function, and normal numbers and relatively normal function of NK cells.

Gene Therapy for Artemis-Deficient SCID

Infants with severe combined immunodeficiency (SCID), a disease characterized by a failure of T-cell development, die of opportunistic infection unless treated. Standard allogeneic hematopoietic-cell transplantation has limitations due to immunologic differences between the patient and the donor. The X-linked form of SCID is caused by hemizygous damaging variants in the gene *IL2RG* (encoding the γ chain of the interleukin-2 receptor), and adenosine deaminase-deficient SCID (ADA-SCID) is caused by biallelic damaging variants in the gene *ADA* (which encodes adenosine deaminase). Both disease types have been successfully treated with autologous gene therapy

Earlier gene-therapy studies for SCID

SCID Type	Gene	Vector Backbone	Promoter	Use of an Insulator	Use of Native or Codon-Optimized Transgene	Busulfan Dose Given or Targeted Exposure	Safety Issues	ClinicalTrials.gov Number
X-linked	<i>IL2RG</i>	γ RV	Viral LTR	No	Native	0	Yes ^{1,†}	NCT01410019 NCT01175239
ADA	<i>ADA</i>	γ RV	Viral LTR	No	Native	4 mg/kg	Rare ^{2,‡}	NCT00598481 NCT00599781 NCT03478670 NCT00794508
X-linked	<i>IL2RG</i>	SIN- γ RV	EF1 α short	No	Native	0	None to date	NCT01129544 NCT01175239 NCT01410019
X-linked	<i>IL2RG</i>	SIN-LV	EF1 α short	Yes	Codon-optimized	22 mgxhr/liter	Possible ^{4,§}	NCT01306019 NCT01512888
X-linked	<i>IL2RG</i>	SIN-LV	EF1 α short	No	Codon-optimized	30 mgxhr/liter	None to date	NCT03311503
ADA	<i>ADA</i>	SIN-LV	EF1 α short	No	Codon-optimized	4 mg/kg	None to date	NCT01852071 NCT02999984 NCT01380990
ART	<i>DCLRE1C</i>	SIN-LV	Artemis	No	Native	20 mgxhr/liter	None to date	NCT03538899

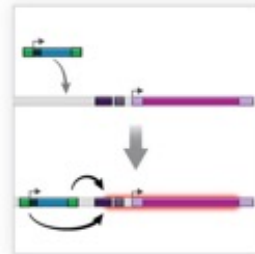
What does Artemis do?

The development and function of T and B cells are dependent on variable (V), diversity (D), and joining (J) gene recombination, a process that generates antigen-specific unique T-cell and B-cell receptors. After the lymphocyte-specific recombination-activating genes 1 (*RAG1*) and 2 (*RAG2*) make **double-stranded breaks** in the VDJ regions of the genes encoding T-cell and B-cell receptors, Artemis (an endonuclease involved in general DNA repair) becomes activated, which allows the **rejoining of the cut ends** and expression of the rearranged receptors. Deficiency of ***RAG1*, *RAG2*, or *Artemis*** result in a failure of T-cell and B-cell development.



Conditioning

A term used to describe a course of treatment comprising one or more medications administered to patients before transplantation of allogeneic or autologous hematopoietic stem cells (HSCs). Typically, alkylating agents such as busulfan that eliminate the recipient's HSCs are given to “make space” for the transplanted cells. For most allogeneic transplant recipients, additional agents are given to eliminate immune cells and prevent immunologic rejection of the graft.



Insertional oncogenesis

An induction of hematologic cancer caused by vector insertion. Integrating viruses insert into different chromosomal locations in each infected cell and according to patterns specific to the type of virus. Gamma retroviruses have been associated with insertional oncogenesis in trials of gene therapy that use HSCs as a result of their tendency to insert near the transcriptional start site of genes, induce aberrant expression of the neighboring gene, and potentially give that clone a survival advantage. Lentiviruses tend to insert within the coding regions of genes. Reports of insertional oncogenesis have been rare, as have reports of clonal expansion due to aberrant splicing associated with insertion of a transgene.

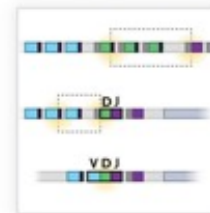
Why Is ART-SCID Hard to Treat?

Because Artemis is critical to the general response to radiation and other inducers of DNA damage (such as busulfan, which is typically used in conditioning regimens), patients with ART-SCID have clinical manifestations outside the immune system and are susceptible to greater toxic effects. An additional challenge is that patients with ART-SCID, unlike patients with some other forms of SCID, require conditioning for engraftment. (Conditioning involves the depletion of the bone marrow to create space for the adoptively transferred stem cells). Particular complications, such as dental abnormalities, poor growth, and endocrinopathies, may occur with higher frequency in patients with ART-SCID because conditioning induces DNA damage.



Synthetic promoters

Genetic sequences composed of regulatory elements not usually found together in nature that drive the expression of an adjacent gene. These elements can include promoter fragments, enhancers, or microRNA-binding sites or can be newly engineered.

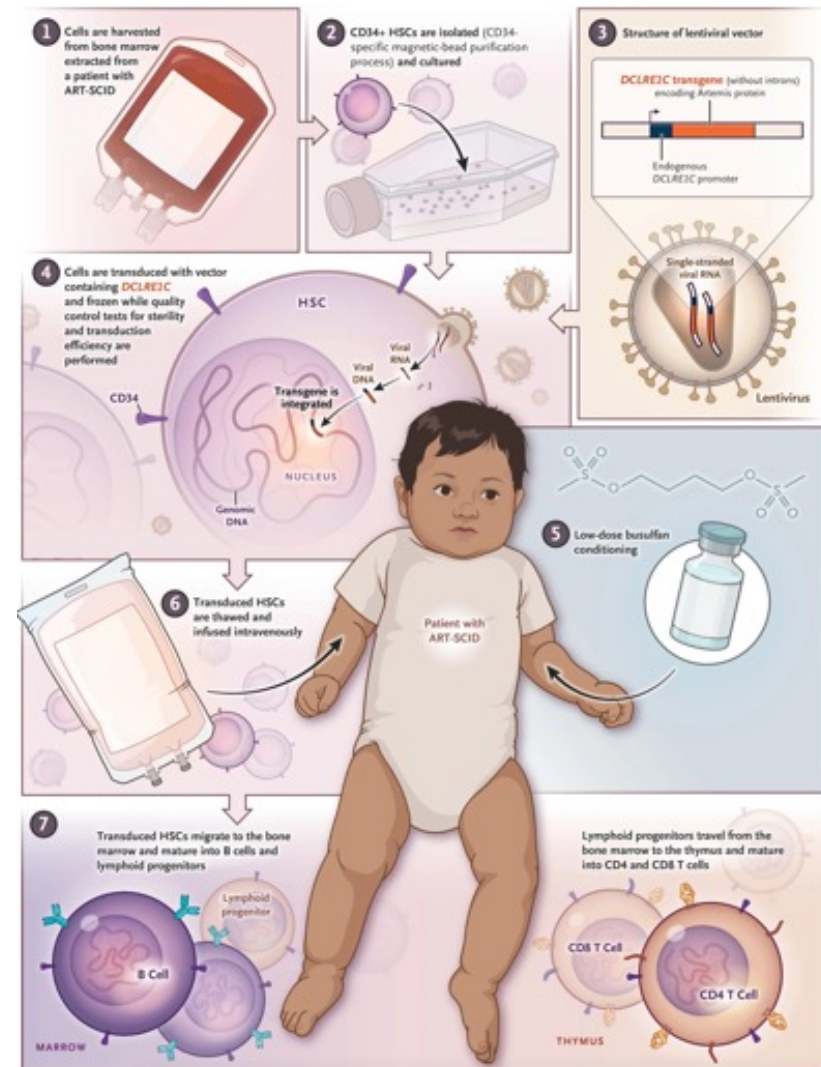


VDJ recombination

A process involving the cutting and rejoining of the loci encoding T-cell and B-cell receptors. These loci are highly polymorphic and contain multiple variable (V), diversity (D), and joining (J) regions, flanked by recombination signal sequences (RSS). Each developing T and B cell rearranges the locus to generate a unique transcript containing one V, one D, and one J region, a process known as VDJ recombination. The RAG1–RAG2 protein complex begins this process by cutting at RSS sites.

How Was Gene Therapy Carried Out?

Cowan et al. used an **integrating viral vector** to bring about **gene “addition”**. Gene addition takes advantage of the natural properties of certain types of viruses, including the lentiviruses, to integrate into the patient’s genome in a semirandom fashion. Cowen et al. **removed the coding genes from a lentivirus**, **replaced them with *DCLRE1C***, and then infected the patient’s own long-term **hematopoietic stem cells** (HSCs) with the viral vector. Successful integration into the genome of a given HSC allows the therapeutic gene to be propagated to all mature blood progeny of that cell.



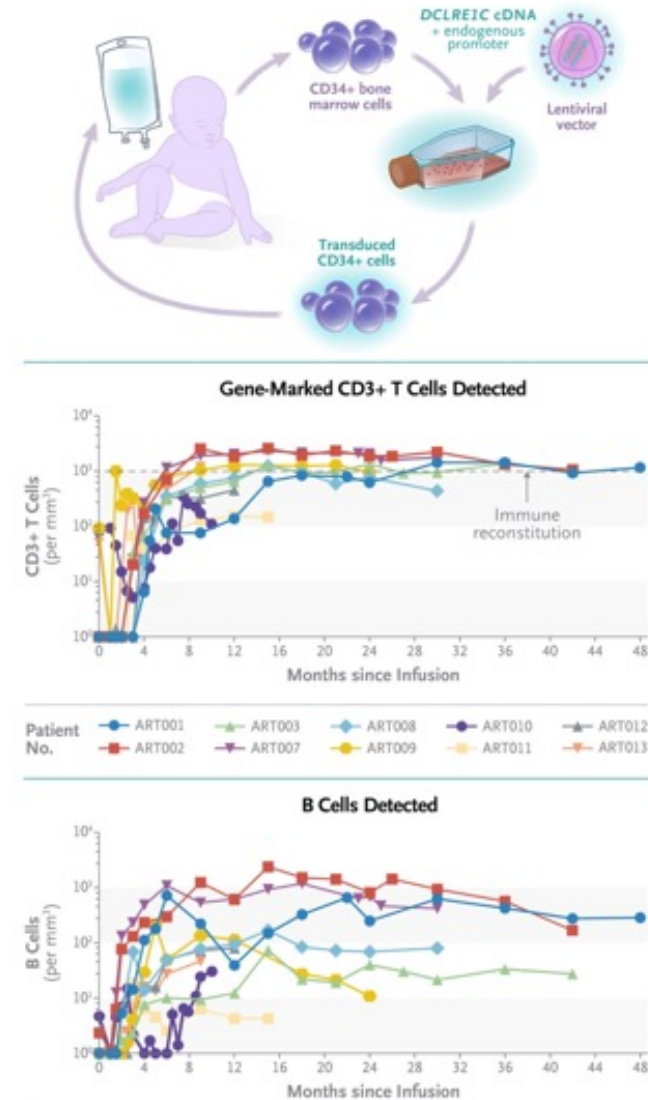
Autologous bone marrow–derived CD34+ hematopoietic stem cells (HSCs) from patients with Artemis-deficient severe combined immunodeficiency (ART-SCID) were transduced with a lentiviral vector engineered to express the *DCLRE1C* transgene under the control of the endogenous *DCLRE1C* promoter. Cells were frozen, and tests of sterility and transduction efficiency were performed. Patients received low-dose busulfan conditioning and thawed transduced HSCs were infused. Transduced HSCs carrying the integrated *DCLRE1C* transgene developed into B and T cells in the bone marrow and thymus, respectively.

Any Special Features of the Gene-Therapy Trial?

A novel feature of this gene-therapy trial is the use of an endogenous gene-specific promoter to control gene expression. Cowan et al. used the **regulatory DNA element that is normally adjacent to *DCLRE1C*** (rather than a viral regulatory element or promoter from another human gene, for example). **Previous experiments have shown that it is important to have just the right amount of Artemis: not too much and not too little.** The endogenous promoter seemed to be a good choice for obtaining physiologic expression and avoiding toxic effects inflicted by overexpression. A recent report implicating a strong viral promoter in the occurrence of insertional oncogenesis in a trial of lentiviral gene therapy for adrenoleukodystrophy further underscores the safety of an endogenous weaker promoter. Other recently developed vectors have transgenes that have been “codon-optimized.” This process involves changing nucleotides in the sequence in a way that favors codons that are highly represented in mammalian cells, thereby leading to higher levels of protein per copy of transgene. Codon optimization takes advantage of redundancy in the genetic code; the new codons are synonymous with those they replace. Cowan et al., however, did not alter the therapeutic copy of *DCLRE1C* because they were striving for a physiologic level of expression. The fact that most of the T and B cells in the patients had three or more copies of therapeutic *DCLRE1C*, rather than the two copies of normal cells, suggests that true endogenous expression was not achieved and that at some point during development, three or more copies were required to permit maturation of the lymphocyte.

Lentiviral Gene Therapy for Artemis-Deficient SCID

The DNA-repair enzyme Artemis is essential for rearrangement of T- and B-cell receptors. Mutations in *DCLRE1C*, which encodes Artemis, cause Artemis-deficient severe combined immunodeficiency (ART-SCID), which is poorly responsive to allogeneic hematopoietic-cell transplantation. We carried out a phase 1–2 clinical study of the transfusion of autologous CD34+ cells, transfected with a lentiviral vector containing *DCLRE1C*, in 10 infants with newly diagnosed ART-SCID. We followed them for a median of 31.2 months.



CONCLUSIONS

Among infants with newly diagnosed Artemis-deficient severe combined immunodeficiency, infusion of autologous lentiviral gene-corrected CD34+ bone marrow cells after conditioning with low-dose busulfan resulted in gene-corrected, functional T cells and B cells and the expected grade 3 or 4 adverse events with chemotherapy.

Severe combined immunodeficiency (SCID), characterized by a lack of T lymphocytes with a lack of or nonfunctional B lymphocytes, is genetically heterogeneous: it is caused by a defect in any one of approximately 20 genes. Population-based newborn screening has established that SCID occurs in approximately 1 in 65,000 births (95% confidence interval, 1 in 51,000 to 1 in 90,000) in the United States. Artemis-deficient SCID (ART-SCID), resulting from mutations in the gene *DCLRE1C* (DNA cross-link repair 1C), constitutes 2 to 3% of all SCID. It has a high incidence among persons of Navajo or Apache descent and in certain consanguineous populations and shows poor response to treatment by allogeneic hematopoietic-cell transplantation (HCT). In the absence of normal levels of functional Artemis protein, the repair of double-strand DNA breaks is compromised, which results in a T-cell–negative, B-cell–negative, natural killer (NK) cell–positive immunophenotype — arising from arrested V(D)J recombination of T and B lymphocytes — and increased systemic sensitivity to alkylating agents typically used as pre-HCT conditioning.

Patients and intervention

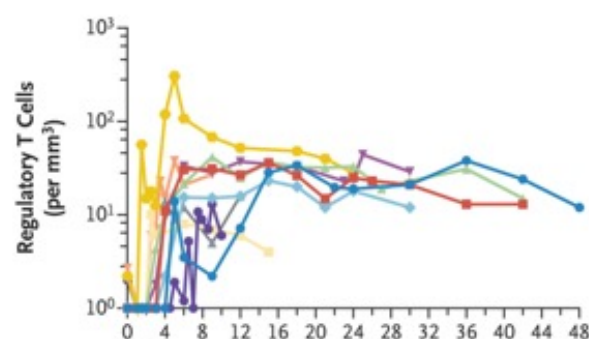
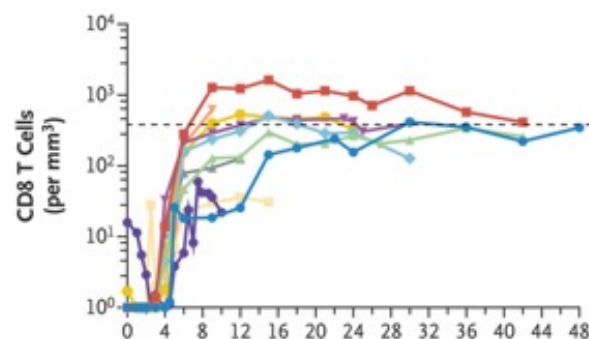
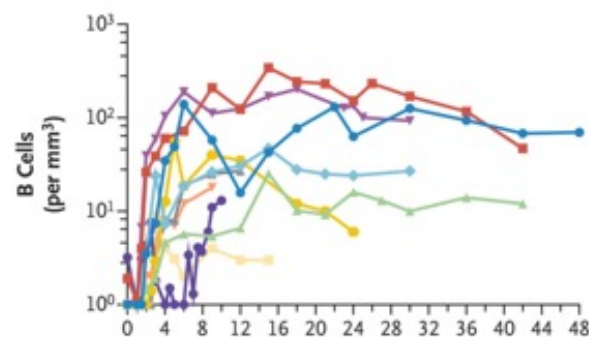
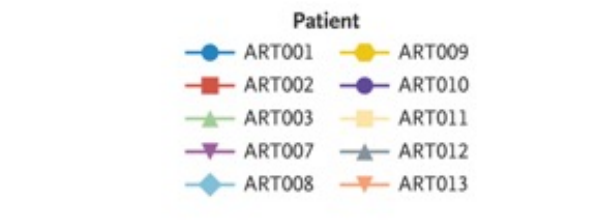
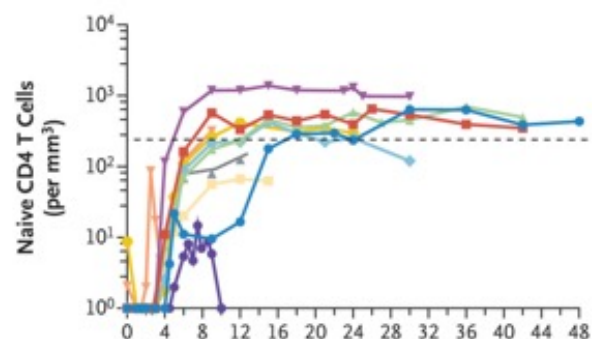
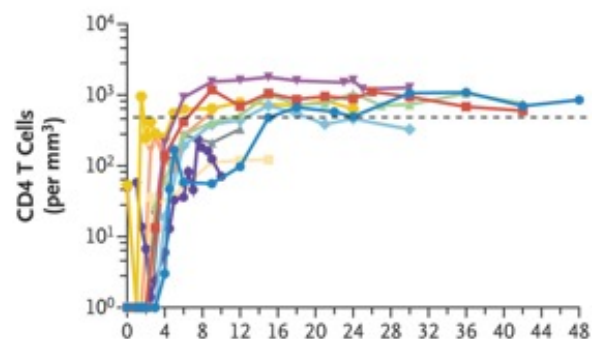
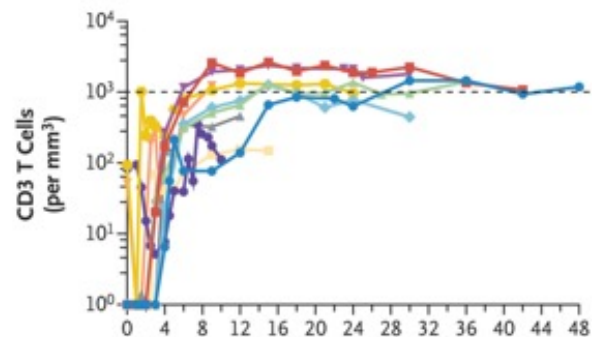
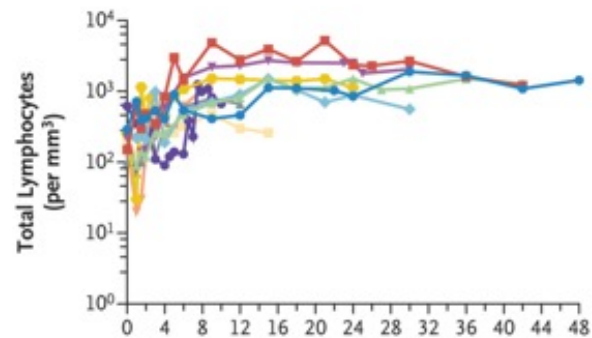
Ten infants with newly diagnosed ART-SCID who lacked an HLA-matched sibling donor were enrolled and treated at UCSF between June 2018 and September 2021. Three older patients with insufficient immunity after allogeneic HCT were also treated; data from these patients are being analyzed.

Product Manufacturing

The AProArt vector, described previously, was produced at the University of Indiana Vector Production Facility. Bone marrow (20 ml per kilogram of body weight) that was collected while the patient was under general anesthesia was enriched for CD34+ cells (CliniMACS machine, Miltenyi Biotec) according to the manufacturer's instructions. The CD34+ cells were cultured overnight in RetroNectin (Takara Bio)–coated plates with recombinant human thrombopoietin, human stem-cell factor, human Fms-like tyrosine kinase receptor 3 ligand, and interleukin-3. The cells were transduced with AProArt for 6 to 8 hours on each of the following 2 days, after which they were cryopreserved in liquid nitrogen, with aliquots reserved for testing.

Patient Characteristics and Disease Course.

Variable	Patient ART001	Patient ART002	Patient ART003	Patient ART007	Patient ART008	Patient ART009	Patient ART010	Patient ART011	Patient ART012	Patient ART013
Sex	Male	Female	Female	Male	Female	Male	Male	Male	Female	Male
Race or ethnic group†	Navajo	Hispanic	Hispanic/White	White	Navajo	Navajo	Vietnamese	Hispanic/Japanese	Lebanese	Apache/Navajo
DCLRE1C mutation, chromosome 10p13	Hom c.597C→A (p.Tyr199X)	Hom del exons 1–4 (82 kb)	Del exons 1–3‡	Del exons 1–5 (82 kb); c.406G→A (p.Asp136Asn)	Hom c.597C→A (p.Tyr199X)	Hom c.597C→A (p.Tyr199X)	Del exons 1–3; c.47T→C (p.Ile16Thr)	Del exon 3; del exons 1–3	c.161+2T→G (splice); c.346T→C (p.Cys116Arg)	Hom c.597C→A (p.Tyr199X)
Clinical findings before GT										
NBS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
SCID neutropenia§	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes
Other	Rhinovirus; noninfectious oral ulcers				Noninfectious oral ulcers	Maternal chimerism with GVHD of skin¶	CMV viremia	Preterm birth at 31 wk of gestation; grade 1 bilateral intraventricular bleeding	Maternal chimerism with GVHD of skin and liver¶	Maternal chimerism with GVHD of skin¶
Clinical findings after GT	Noninfectious oral ulcers; central-catheter bacteremia; Cd and norovirus enteritis; all resolved	CMV treated with valganciclovir; RVE; acalculous cholangitis treated with CCE; all resolved	None	None	Noninfectious oral ulcers, resolved; behavior suggestive of autism	Persistent maternal GVHD, resolved	CMV encephalitis treated with multiple antiviral agents; noninfectious oral ulcers; all resolved	None	Persistent maternal GVHD; noninfectious oral ulcers; Cd colitis; intestinal bleeding from sirolimus; all resolved	Persistent maternal GVHD, resolved
Age at cell infusion (mo)	2.6	3.7	3.0	2.3	2.5	2.4	2.5	3.8	13.3	2.3
Busulfan cAUC (mg×hr/liter)	17.6	19.9	18.8	19.7	18.6	18.9	19.2	20.2	19.4	18.9
Busulfan dose (mg/kg)	2.5	4.0	3.7	3.5	4.1	3.8	2.9	2.8	2.0	4.1
CD34+ cell dose (×10 ⁴ /kg)	6.6	3.9	6.0	10.6	6.1	12.1	10.4	9.9	2.2	8.8
Mean VCN (copies/cell)	1.9	1.9	3.9	2.3	1.8	3.2	2.9	3.4	1.6	2.6
TDE (%)	68	66	84	81	65	81	81	82	62	74
Postbusulfan lowest ANC (cells/mm ³)	1370	1020	170	260	490	350	190	450	140	80
Time of postbusulfan lowest ANC (days)	13	19	19; G	18; G	14	18	14; G	20; G	21; G	14; G
Follow-up after GT (mo)	48.9	45.2	43.9	34.5	33.4	28.9	12**	17.8	14.5	10.0



Months since Infusion

Lymphocytes and Lymphocyte Subsets after Infusion of Autologous Lentiviral-Transduced CD34+ Cells.

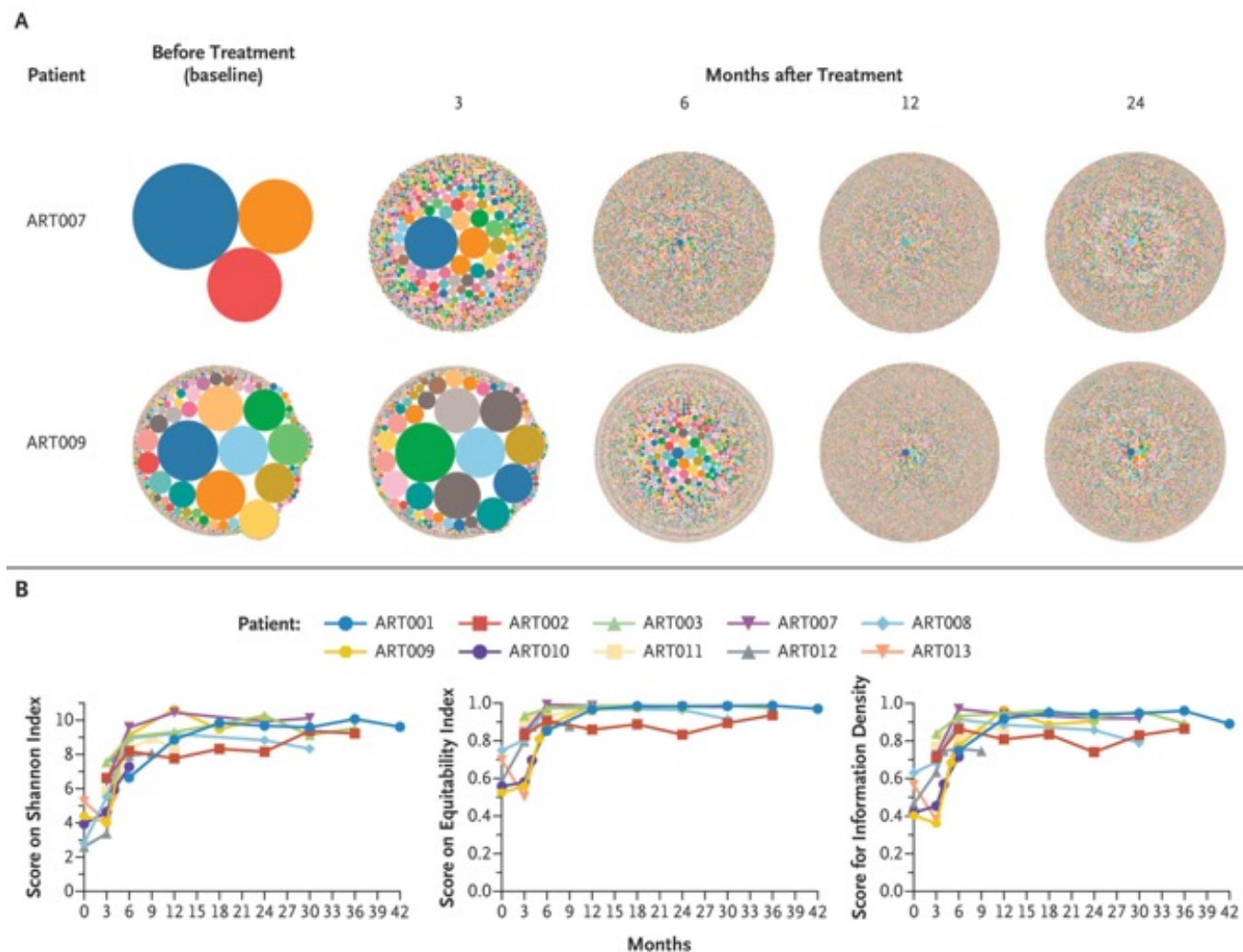
Shown are cells per cubic millimeter of peripheral blood. The values that were used to define T-cell immune reconstitution (dashed lines) are as follows: CD3 T cells, more than 1000 per cubic millimeter; CD4 T cells, more than 500 per cubic millimeter; CD8 T cells, more than 300 per cubic millimeter; and naive CD4 T cells, more than 200 per cubic millimeter.^{7,13} The mean number of regulatory T cells for children 10 to 48 months of age is 60 per cubic millimeter (range, not available).²³

Immune Status at Last Follow-up after Infusion of Lentiviral-Transduced Hematopoietic Stem Cells.

Variable	Patient ART001	Patient ART002	Patient ART003	Patient ART007	Patient ART008	Patient ART009	Patient ART010	Patient ART011	Patient ART012	Patient ART013
Most recent laboratory follow-up (mo after cell infusion)	48	43	42	30	31	25	12†	18	13	10
Lymphocyte subsets										
CD3 >1000 cells/mm ³	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes
CD4 >500 cells/mm ³	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes
CD19 cells detectable (cells/mm ³)	Yes (128)	Yes (73)	Yes (11)	Yes (144)	Yes (34)	Yes (8)	Yes (20)	Yes (2)	Yes (40)	Yes (28)
Naive CD4+ cells >20% of CD4+ cells (%)‡	Yes (49)	Yes (59)	Yes (68)	Yes (77)	Yes (37)	Yes (45)	No (16)	Yes (51)	Yes (34)	Yes (61)
PHA response >100% LLN										
CD45+ lymphocytes	Yes§	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
CD3+ T cells	Yes§	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
IgA (mg/dl)	27	55	36	44	<7	<7	<7	<7	24	<7
IgM (mg/dl)	59	29	18	90	152	26	6	15	65	16
IgM IHG titer¶	1:16	1:32	1:2	<1:2	1:32	1:2	1:1	Not tested	<1:2	1:2
IgG infusions stopped (mo)**	Yes (32); K	Yes (19); K, L	No	Yes (20); K, L	Yes (30)	No	No	No	No	No
Infections, response										
		CMV after treatment, resolved					Persistent CMV from before treatment			
AIHA (mo that treatment stopped)	Yes (32)	Yes; never treated	No	No	No	Yes (11)	Yes	No	No	No

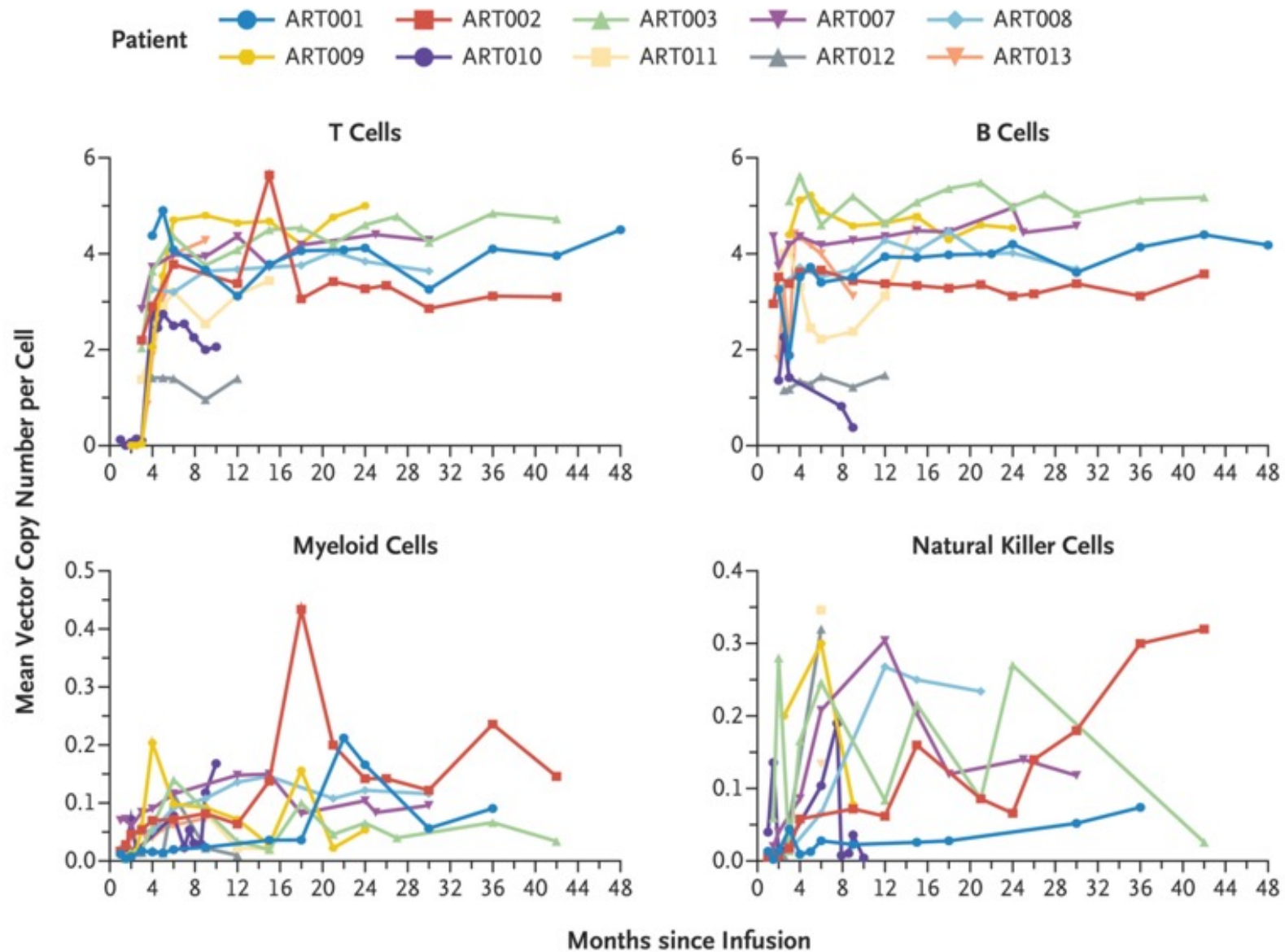
Diversity of T-Cell Receptor β -Chain Variable Sequences at Baseline and after Infusion of CD34+ Gene-Corrected Cells.

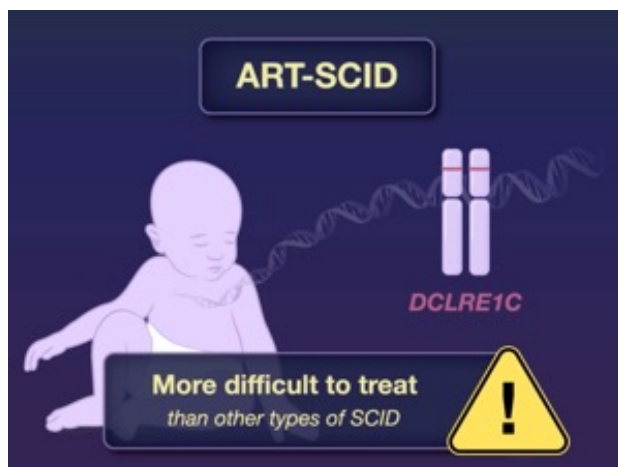
Panel A shows hierarchical tree maps of sequence diversity in Patients ART007 and ART009 from baseline to 36 months after infusion. Panel B shows serial measurements of scores on the Shannon index (the range includes all numbers >0), scores on the equitability index (range, 0 to 1), and scores for information density (range, 0 to 1); for all three scales, higher values indicate greater diversity. Scores on all three scales increased during the first 6 to 12 months after infusion, and these increases were then sustained.



Gene Marking in Peripheral Blood Cells after Infusion of Autologous Lentiviral-Transduced CD34+ Cells.

Subpopulations of peripheral-blood mononuclear cells were sorted after staining for the following cell-surface markers: T cells, CD3+; B cells, CD19+; myeloid cells, CD14+/CD15+; and natural killer cells, CD3−/CD19−/CD56+.





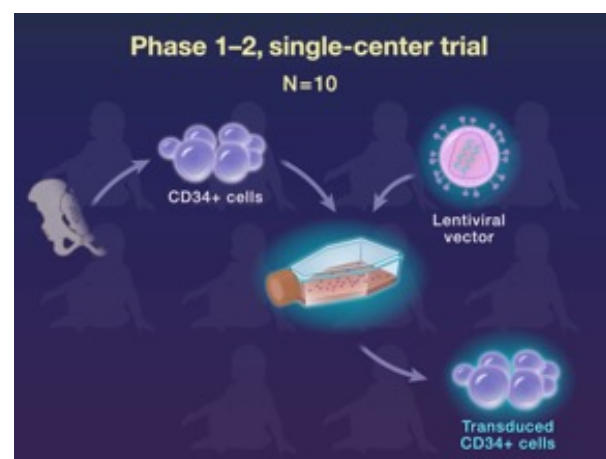
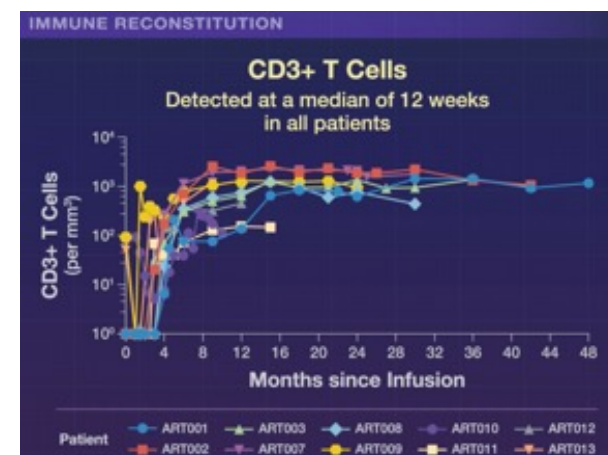
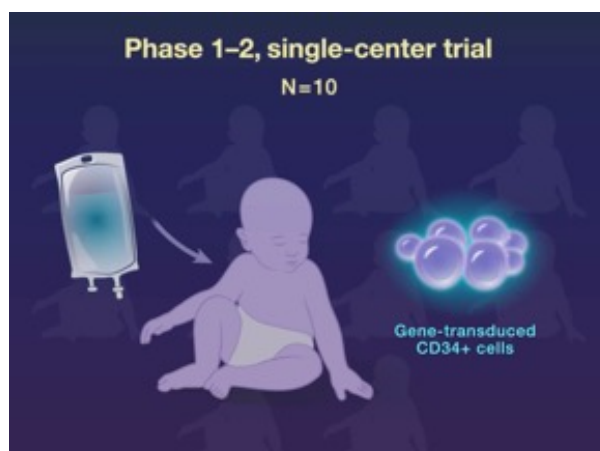
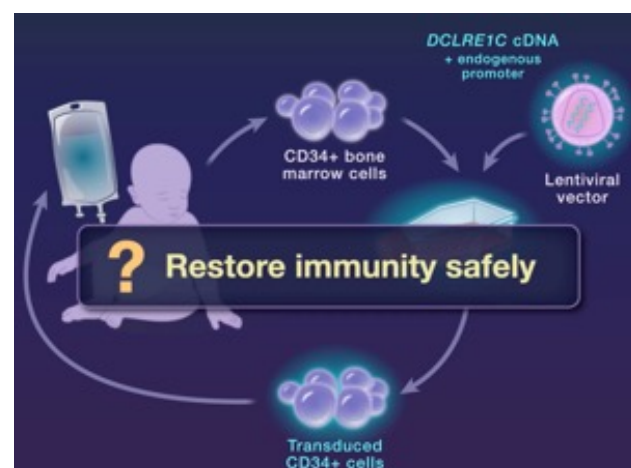
ADVERSE EVENTS

Autoimmune Hemolytic Anemia

- Developed in four patients
4 to 11 months after infusion

	Feb	Mar	Apr
✓			
✗			
✗			
✗			

- Resolved with reconstitution of T-cell immunity

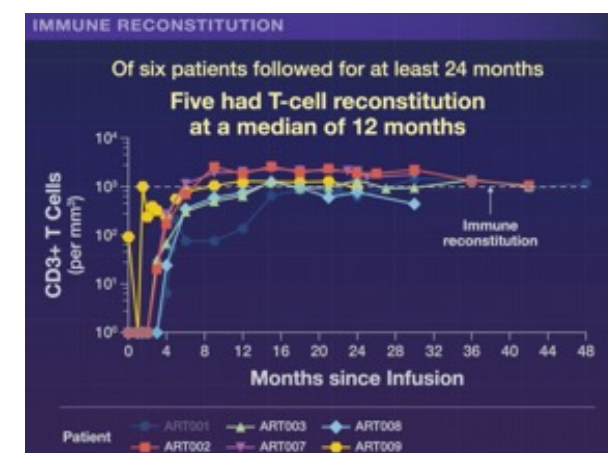


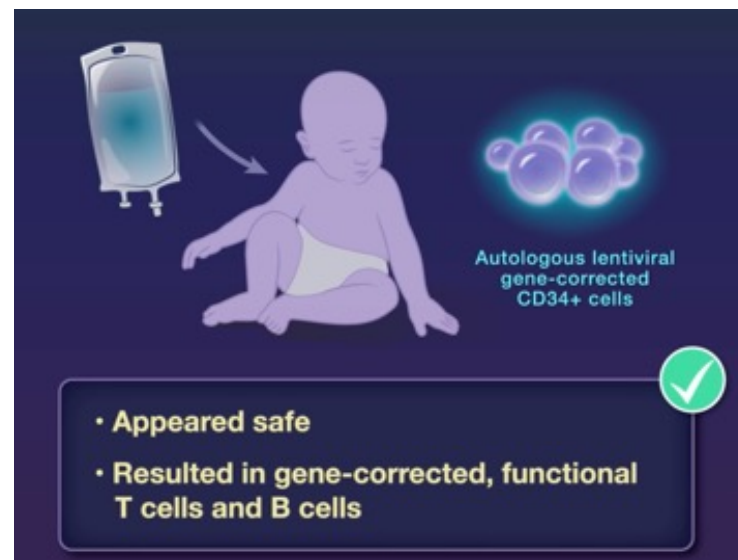
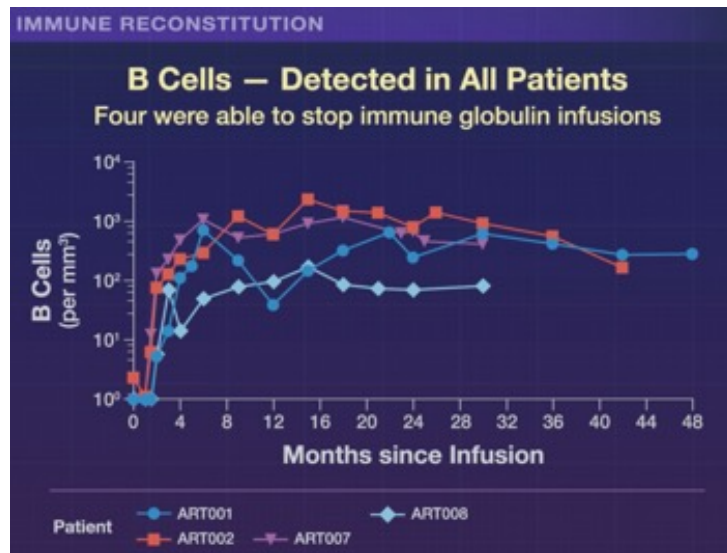
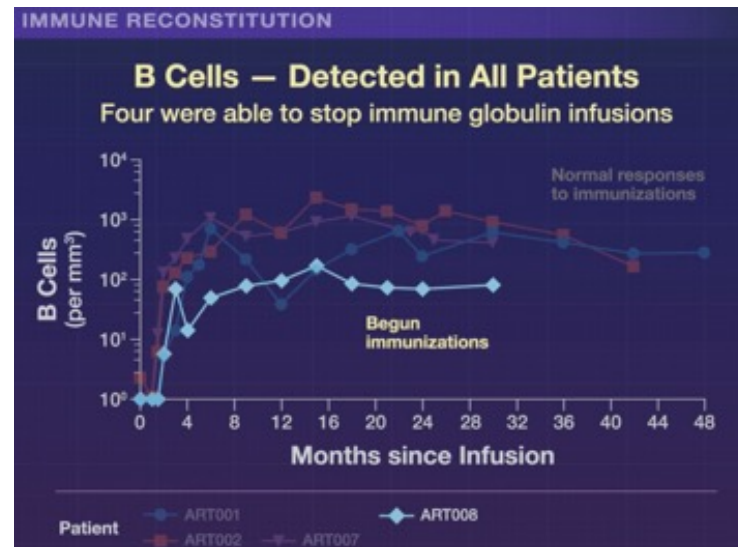
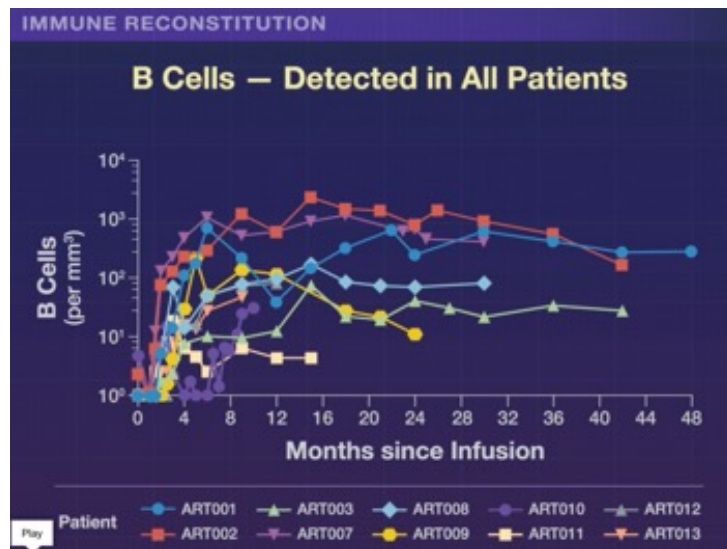
ADVERSE EVENTS

Safety Assessments

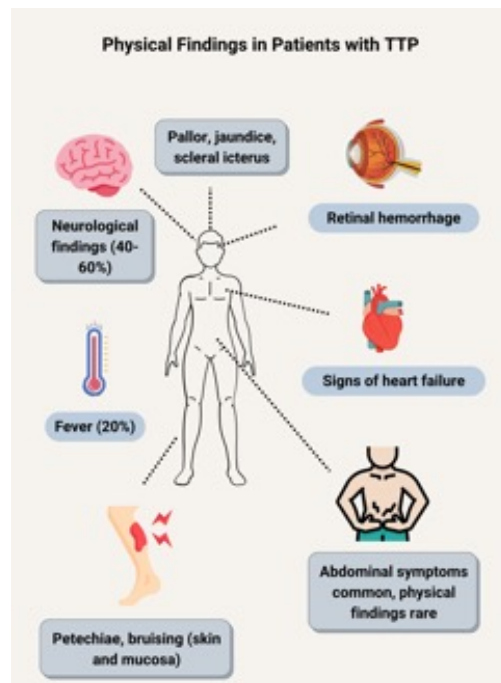
(through day 42 after infusion)

No unexpected adverse events

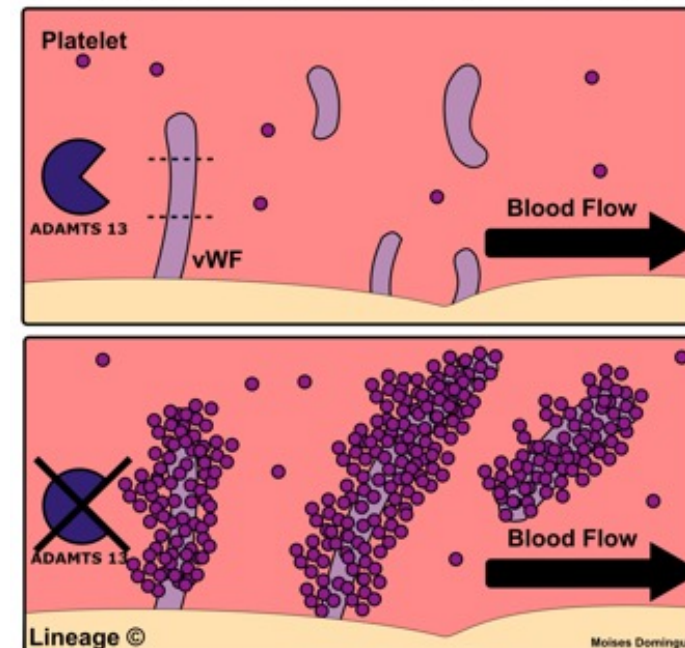




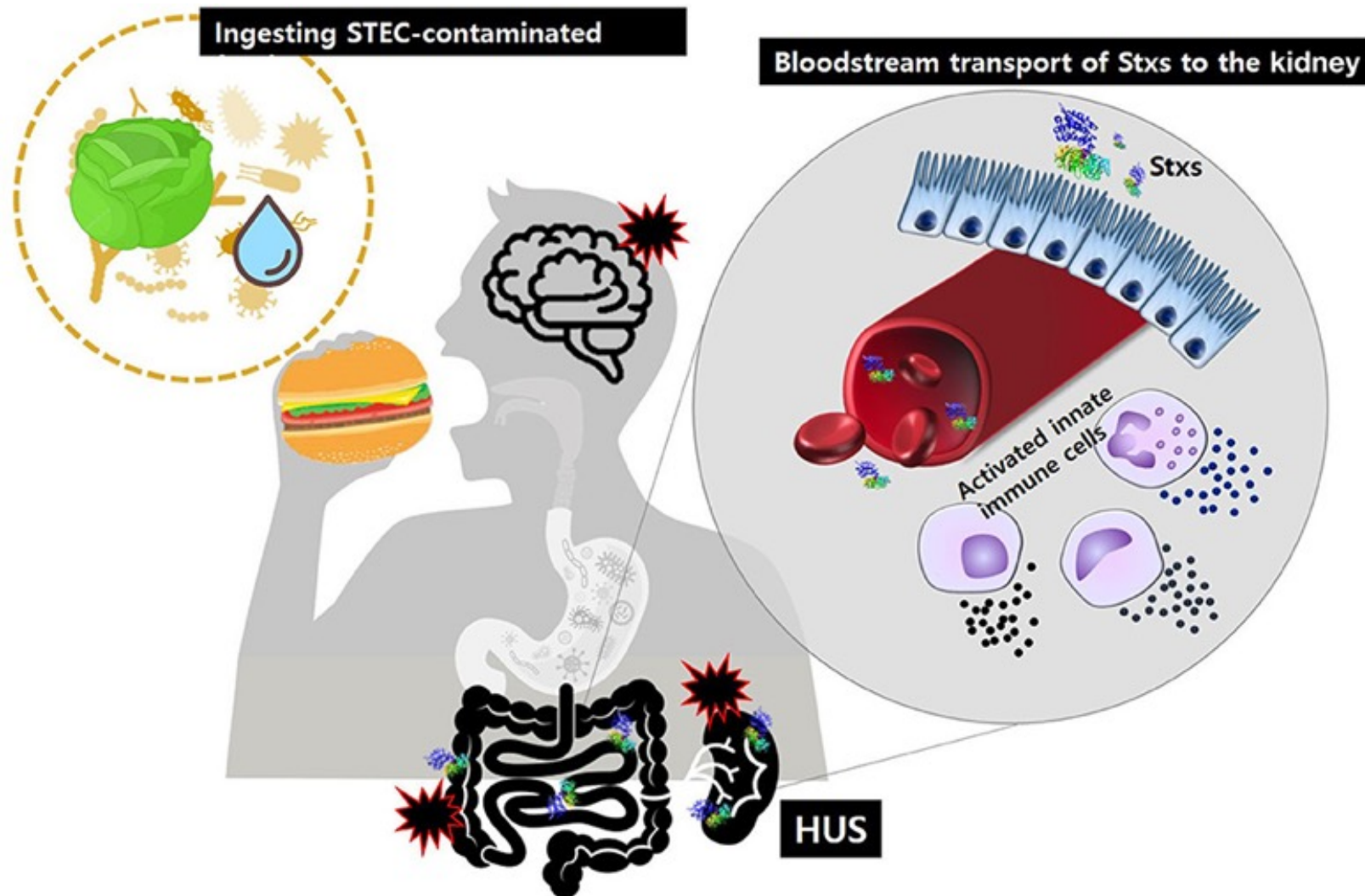
„Thrombotisch“ bedeutet, dass Blutgerinnsel entstehen, „thrombozytopenisch“ heißt, dass die Blutplättchenzahl gering ist und „Purpura“ weist darauf hin, dass purpurfarbene Stellen oder Blutergüsse auf der Haut zu sehen sind. Die **thrombotisch-thrombozytopenische Purpura (TTP)** ist eine seltene Erkrankung, bei der sich plötzlich viele kleine Blutgerinnsel (Thromben) im ganzen Körper bilden. Sie ist mit dem **hämolytisch-urämisches Syndrom (HUS)** verwandt, tritt aber mit einer größeren Wahrscheinlichkeit bei Erwachsenen auf als das HUS, das häufiger bei Kindern auftritt. Die Ursache von TTP ist meistens unbekannt, aber bei manchen Patienten entwickelt sie sich nach der Anwendung gewisser **Medikamente (einschließlich Chinin, Cyclosporin und Mitomycin C)**, nach bestimmten Arten von Darminfektionen, während der Schwangerschaft oder, in **seltenen Fällen, als Erbkrankheit**. Bei den meisten Betroffenen handelt es sich bei TTP um eine Autoimmunerkrankung. Dabei bildet das körpereigene Immunsystem Antikörper gegen ein Enzym (ADAMTS13). Ist dieses Enzym fehlerhaft, klumpen die Blutplättchen in den Blutgefäßen zusammen, die Anzahl der Blutplättchen im Blut (Blutplättchenzahl) sinkt und die betroffenen Organe (wie beispielsweise das Gehirn und die Nieren) können geschädigt werden.



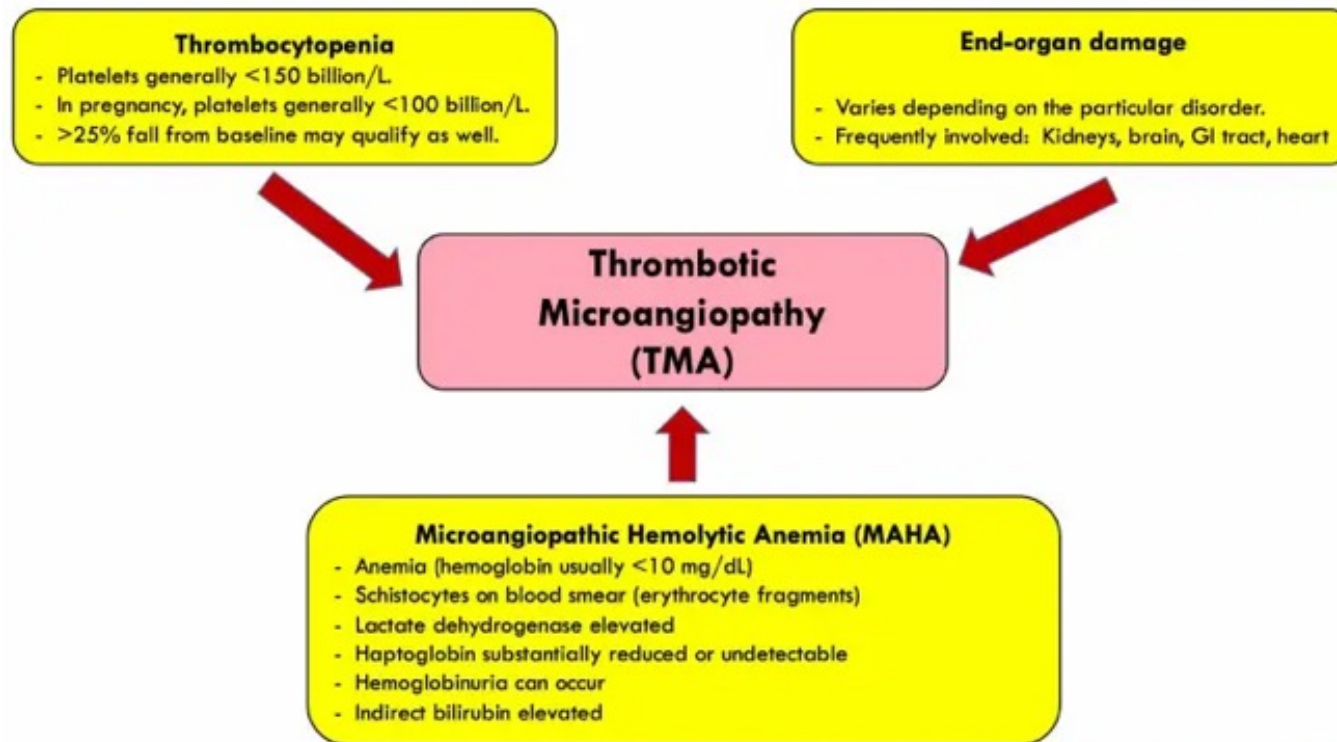
Thrombotic Thrombocytopenic Purpura



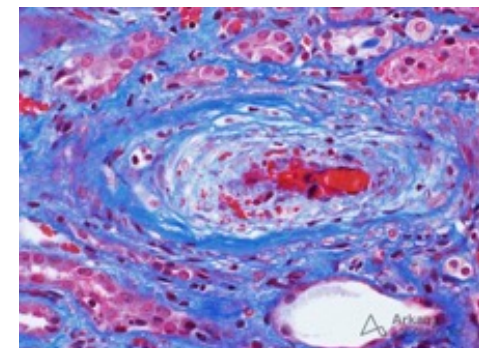
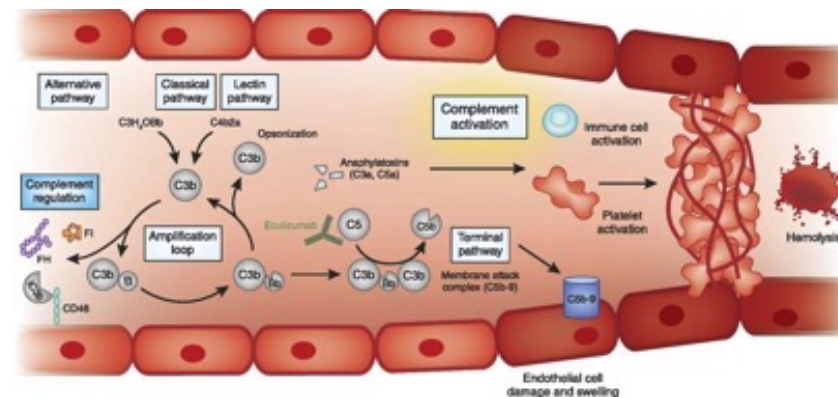
In contrast, STEC is an entirely different disease. After ingestion of food or water contaminated with pathogenic STEC, Stxs may cross the intestinal epithelial barrier via M-cell uptake and transcytosis or paracellular transport. Once in the submucosa, the toxins activate innate immune cells, such as neutrophils or monocytes that act as “carrier” cells to deliver Stxs in the bloodstream and may also further exacerbate tissue injury via localized production of **proinflammatory cytokines**. Ultimately, the toxins are transferred to glomerular endothelial cells and tubular epithelial cells, which are rich in the **toxin receptor Gb3**. Damage to the kidney, the primary target organ, leads to D + HUS (diarrhea-associated hemolytic uremic syndrome).



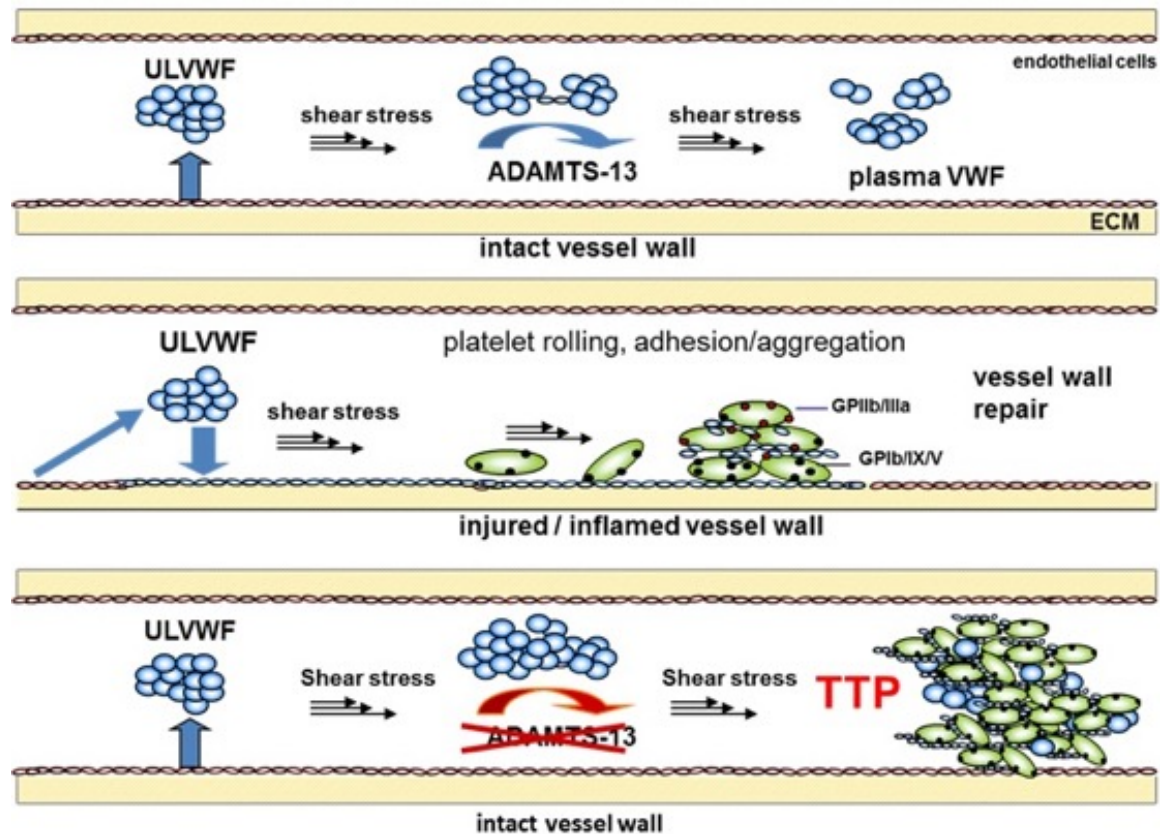
3 components of thrombotic microangiopathy (TMA)



**Both TTP and
STEC cause
thrombotic
microangiopathy**



Structure of ADAMTS13. S, signal peptide domain; P, short propeptide domain; MP, metalloprotease domain; Dis, disintegrin-like domain; 1, thrombospondin-1 repeat (TSP1) domain; Cys, characteristic Cysteine-rich domain; Spacer, spacer domain; CUB, CUB domains.



Recombinant ADAMTS13 for Hereditary Thrombotic Thrombocytopenic Purpura

A 27-year-old patient with a history of severe obstetrical complications and arterial thrombosis received a diagnosis of hereditary thrombotic thrombocytopenic purpura (TTP) due to severe ADAMTS13 deficiency when she presented with an acute episode in the 30th week of her second pregnancy. When the acute episode of hereditary TTP became plasma-refractory and fetal death was imminent, weekly injections of recombinant ADAMTS13 at a dose of 40 U per kilogram of body weight were initiated. The patient's platelet count normalized, and the growth of the fetus stabilized. At 37 weeks 1 day of gestation, a small-for-gestational-age boy was delivered by cesarean section. At the time of this report, the patient and her son were well, and she continued to receive injections of recombinant ADAMTS13 every 2 weeks. (Funded by the Swiss National Science Foundation.)

Hereditary TTP is a rare blood disorder with an estimated prevalence of 0.5 to 2 cases per million population worldwide. Hereditary TTP is caused by biallelic mutations in the gene ADAMTS13 that lead to a severe ADAMTS13 deficiency (ADAMTS13 activity <10% of that in normal plasma).¹ In the absence of ADAMTS13, size regulation of von Willebrand factor is lacking. Platelets bind to persisting ultralarge von Willebrand factor multimers, resulting in microvascular thrombosis with end-organ damage, consumptive thrombocytopenia, and microangiopathic hemolytic anemia with schistocytes on the peripheral-blood smear during acute episodes. Today, more than 200 causative mutations affecting ADAMTS13 have been identified in patients with hereditary TTP. Of particular interest in this case is the p.R1060W mutation, which is associated with residual ADAMTS13 activity in the range of 3 to 6% per allele carried and is prevalent among female patients with hereditary TTP who have a first disease manifestation in pregnancy.

A 27-year-old female patient was first seen at our center at 30 weeks 6 days of gestation in her second pregnancy. Twelve months earlier, **her first pregnancy had ended in the 22nd gestational week** with an intrauterine fetal death, which had been preceded by progressive **thrombocytopenia and intrauterine growth restriction**. Two weeks after the fetal death, **the patient had an ischemic stroke** in the vascular bed of the left middle cerebral artery. Her platelet count at the time was 40,000 per microliter (reference range, 150,000 to 400,000).

Mild thrombocytopenia (platelet count, 92,000 per microliter) and a mildly increased lactate dehydrogenase level were noted. Levels of hemoglobin, haptoglobin, creatinine, and liver enzymes were normal. The ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PIGF), used as a marker of placental dysfunction, was marginally elevated at 38 (reference value, <38). Testing for antiphospholipid antibodies was again negative, and a severe deficiency in ADAMTS13 activity (activity level, 3.9%) confirmed a diagnosis of acute TTP.

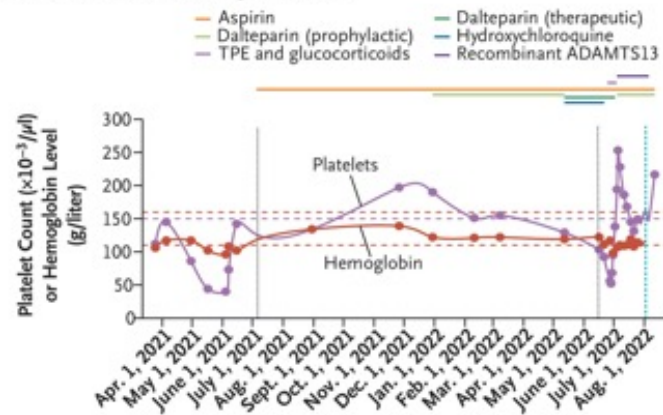
Treatment for the more common immune-mediated TTP, which consists of TPE with replacement of plasma and immunosuppression with methylprednisolone (1 mg per kilogram) was initiated.

At the time of this report, the patient's parents, who have no other children, informed us that the **patient had undergone a neonatal exchange transfusion because of severe hyperbilirubinemia soon after birth**, which adds further evidence for a diagnosis of hereditary TTP. An in-depth medical history for the patient and her family revealed no other previous manifestations of hereditary TTP.

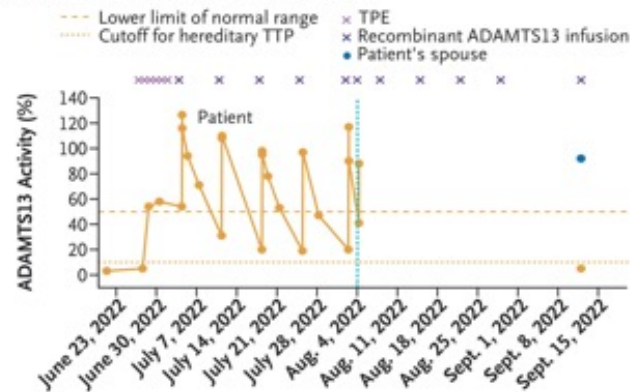
Measurement of ADAMTS13

We measured ADAMTS13 activity with the modified FRETs-VWF73 assay (lower limit of quantification, 1%).^{16,17} Functional ADAMTS13 inhibitors were assessed in a Bethesda-like assay; a value of 0.4 A commercially available enzyme-linked immunosorbent assay (Technoclone) was used to assess anti-ADAMTS13 IgG antibodies; a value of less than 12.1 AU per milliliter indicates a negative result. DNA extraction from leukocytes, amplification of all 29 **ADAMTS13 exons with flanking intron–exon boundaries, and sequencing were performed with the use of standard methods.**

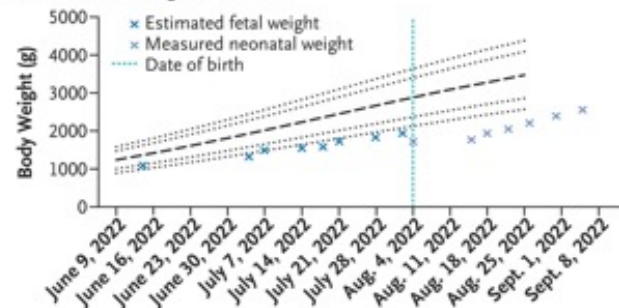
A Platelet Counts and Hemoglobin Levels



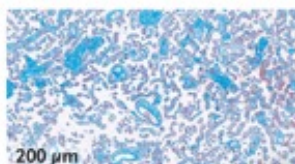
B ADAMTS13 Activity during and after Treatment



C Fetal and Neonatal Weight over Time



D Distal Villous Hypoplasia



E Intervillous Fibrin



Key Maternal and Fetal or Neonatal Measures over Time.

Vertical dotted lines indicate relevant time points: black dotted lines indicate the first stroke (in July 2021) and the second stroke (on June 14, 2022), and the light blue dotted line indicates the cesarean section (date of birth) on August 4, 2022. Panel A shows maternal platelet and hemoglobin concentrations. The horizontal purple dashed line indicates the lower limit of the reference interval for the platelet count, and the horizontal red dashed lines indicate the lower and upper limits of the reference interval for the hemoglobin concentration. The timing of different types of treatment is indicated by solid horizontal lines above the graph. Therapeutic plasma exchange (TPE) was performed daily from June 27 to July 2, 2022. Treatment with recombinant ADAMTS13 was initiated on July 4, 2022. Panel B shows ADAMTS13 activity over time. The lower limit of the normal range for ADAMTS13 activity is 50%, and the cutoff that defines hereditary thrombotic thrombocytopenic purpura (TTP) is 10%. The father of the baby had an ADAMTS13 activity of 92%. Panel C shows estimated and measured fetal weight. Estimated fetal weight was calculated according to the standard of Hadlock et al.¹⁴ The dashed line indicates the 50th percentile, and the dotted lines indicate the 3rd, 10th, 90th, and 97th percentiles. Panels D and E show histopathological features of the placenta (Masson's trichrome staining). Panel D shows the disturbance of regular villous ramifications, characterized by long and slender villi with stretched capillaries arising directly from large stem villi. Panel E shows an area with extensive intervillous fibrin deposition resembling a maternal floor infarction (grayish blue material surrounding necrobiotic villi [deep blue structures]) with complete loss of the trophoblast.

Recombinant ADAMTS13

Recombinant ADAMTS13 is a fully glycosylated recombinant human ADAMTS13 protein produced in a plasma protein-free milieu in a Chinese hamster ovary mammalian expression system. After reconstitution with sterile injection water, the solution has a nominal potency of either 100 U or 300 U per milliliter.

In the phase 1 study, 15 healthy patients with hereditary TTP received a single dose of 5 U, 20 U, or 40 U of recombinant ADAMTS13 per kilogram, designated as the low dose, intermediate dose, and high dose, respectively. In the high-dose group, a mean increment of plasma ADAMTS13 activity of approximately 2 percentage points per unit of recombinant ADAMTS13 administered and a mean terminal half-life of plasma ADAMTS13 activity of approximately 60 hours were documented.

Early on in the patient's course, we contacted the pharmaceutical company that produces recombinant ADAMTS13 for emergency compassionate use and, after the required national approval process, we obtained recombinant ADAMTS13. In a process of shared decision making, the treating physicians involved the patient and her husband in all steps. The couple gave written informed consent for the experimental use of recombinant ADAMTS13, as well as for the publication of the details of the case.

Confirmation of Hereditary TTP

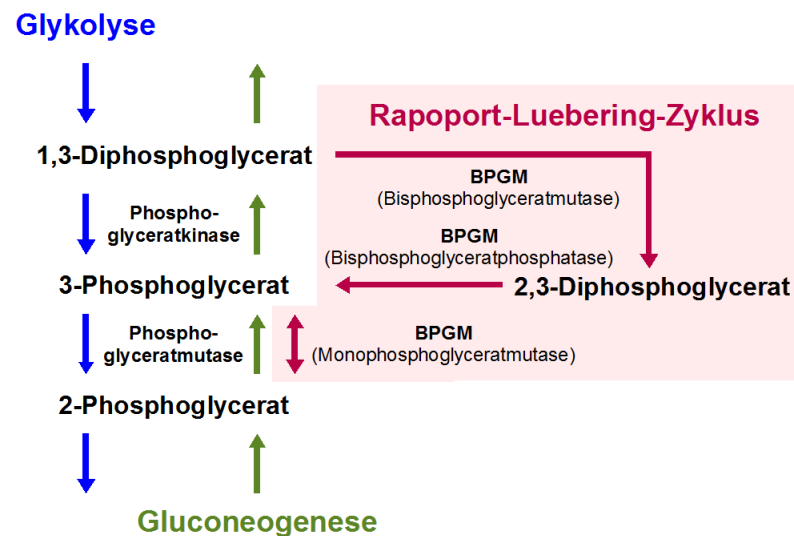
The suspected diagnosis of hereditary TTP was confirmed by the detection of biallelic ADAMTS13 mutations: c.2017A→T (p.I673F) in exon 17 and c.3178C→T (p.R1060W) in exon 24. Both mutations have already been described in other patients with diagnoses of hereditary TTP.²⁻⁵ The patient's baseline ADAMTS13 activity was 3.9%, which conforms to the reported residual ADAMTS13 activity in patients with hereditary TTP who carry one p.R1060W allele.

Discussion

This patient's history is typical of patients with hereditary TTP. In her first days of life, extreme hemolysis associated with severe hyperbilirubinemia made neonatal exchange transfusion necessary, a measure that is taken in 35 to 45% of patients with hereditary TTP. Although concomitant thrombocytopenia is frequent, hereditary TTP is often not considered. Severe obstetrical complications with early preeclampsia (often starting before gestational weeks 20 to 26) are typical of so-called adult-onset hereditary TTP, as is intrauterine growth restriction up to fetal death, as was seen in the patient described here. Arterial thromboses, particularly transient ischemic attacks and ischemic strokes, can occur at a young age in patients with hereditary TTP, with 20% of patients affected at the end of the second decade of life and 50% in the fifth decade. Obstetrical complications, along with arterial thromboses at a relatively young age, are clinical features that overlap with those of antiphospholipid syndrome; these features also overlap with those of "noncriteria" antiphospholipid syndrome, in which tests for antiphospholipid antibody are negative. During acute episodes or at presentation with an acute arterial thrombotic event, thrombocytopenia and microangiopathic hemolytic anemia may be mild in patients with hereditary TTP. The clinical picture may thus be closer to an antiphospholipid syndrome than to classic immune-mediated TTP. Now that ADAMTS13 assays are widely available, we believe that in any newborn who receives a neonatal exchange transfusion or has severe hyperbilirubinemia together with thrombocytopenia, as well as before a diagnosis of seronegative antiphospholipid syndrome is made, a determination of ADAMTS13 activity should be mandatory in order to prevent a delayed diagnosis of hereditary TTP, as well as to prevent the use of futile and potentially harmful treatments.

Der **Rapoport-Luebering-Zyklus**, auch als Rapoport-Luebering-Shunt, Rapoport-Luebering-Shuttle, Phosphoglyceratzyklus oder **2,3-BPG-Zyklus** bezeichnet, ist in der Biochemie ein vor allem in roten Blutkörperchen (Erythrozyten) von Säugetieren ablaufender Stoffwechselweg, also eine Abfolge von enzymatisch gesteuerten chemischen Reaktionen. Es handelt sich um einen aus drei Teilreaktionen bestehenden Nebenweg der Glycolyse, die für die **Energiegewinnung** und den **Kohlenhydratstoffwechsel** fast aller Lebewesen von zentraler Bedeutung ist. Der Rapoport-Luebering-Zyklus gehört somit zu den biochemischen Prozessen zum **Abbau von Traubenzucker im tierischen Organismus**.

Seine Hauptreaktion ist die durch das Enzym Bisphosphoglyceratmutase gesteuerte Bildung des Zwischenprodukts **2,3-Bisphosphoglycerat (2,3-BPG)** aus dem in der Glycolyse entstehenden 1,3-Bisphosphoglycerat. Das im Rapoport-Luebering-Zyklus entstehende **2,3-BPG** wirkt als wichtiger biochemischer Effektor in der Regulation der **Bindungsfähigkeit (Affinität) des Blutfarbstoffs Hämoglobin für das Atemgas Sauerstoff**, insbesondere für deren längerfristige Anpassung an Sauerstoffmangelzustände, und ist damit für die Freisetzung des Sauerstoffs aus den Erythrozyten ins Gewebe von Bedeutung. Es ist darüber hinaus an der enzymatischen Steuerung der Glycolyse beteiligt und fungiert in den Erythrozyten als Energie- und Phosphatspeicher.



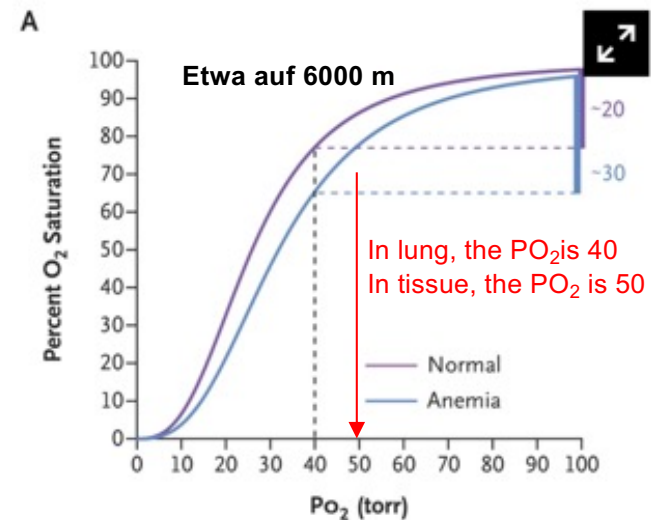
Oxygen Delivery in the Treatment of Anemia

Physiology

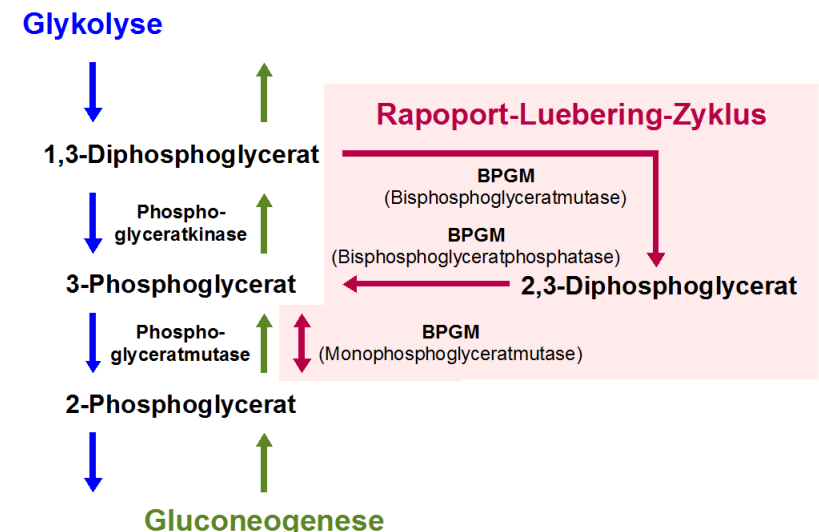
Nearly all patients with anemia, regardless of the cause, have elevated red-cell 2,3-BPG levels.

This adaptation greatly enhances oxygen delivery. At any given oxygen tension (measured as the partial pressure of oxygen [P_{O_2}]), the oxygen saturation is reduced in a person with anemia. Arterial blood normally has a P_{O_2} of about 95 torr (or 95 mm Hg) and is nearly 100% saturated with oxygen. As red cells pass from an arteriole through its capillary bed to its vein, oxygen is released to respiring cells. At a venous P_{O_2} of 40 torr, the oxygen saturation is about 80%. Thus, approximately 20% of the oxygen in the blood is unloaded.

In contrast, in patients with anemia and elevated levels of red-cell 2,3-BPG, the lower oxygen affinity of the blood allows a much higher fraction of the oxygen (about 30%) to be unloaded. This benefit can be shown quantitatively by considering oxygen-carrying capacity rather than hemoglobin levels.

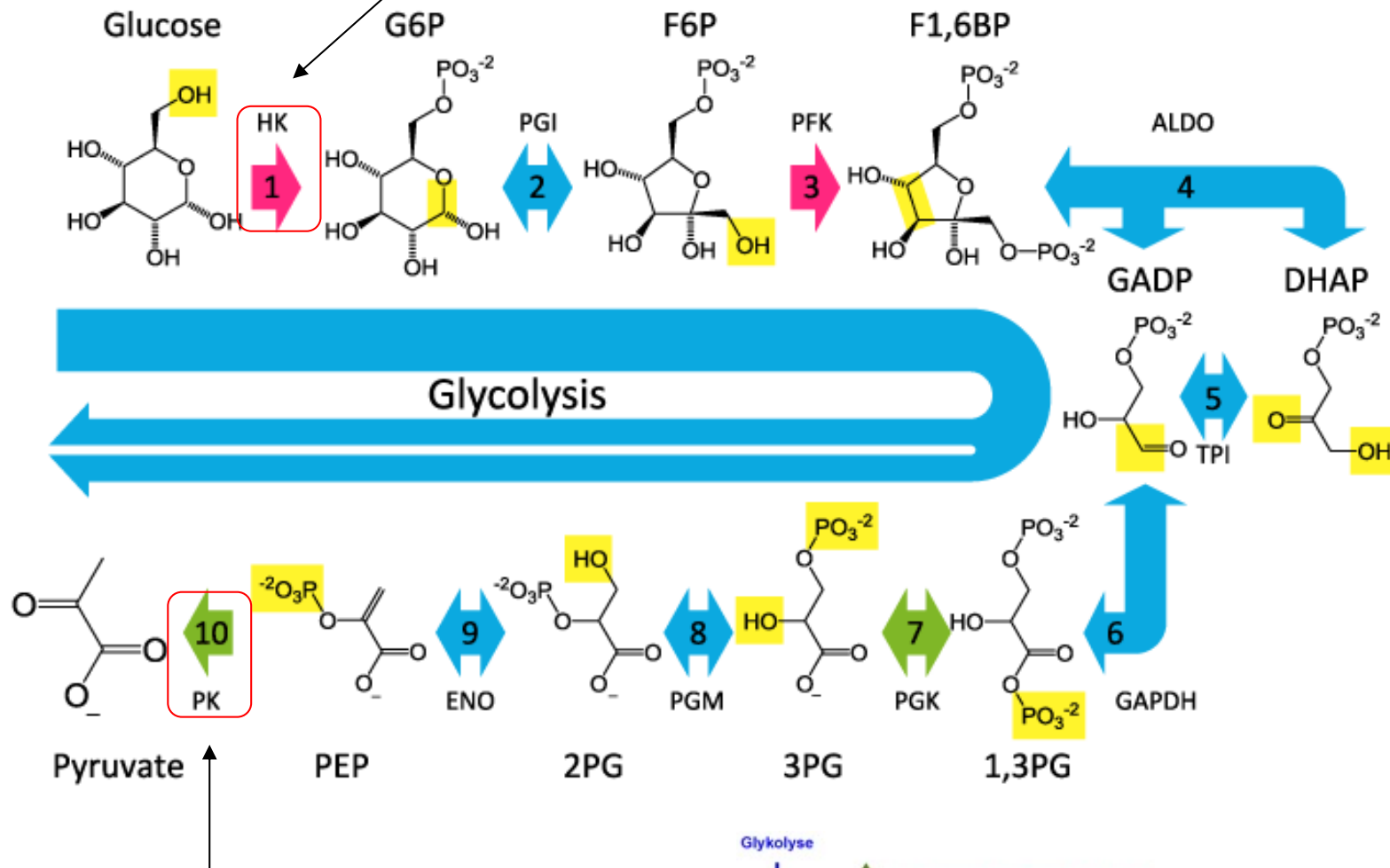


The red cells in humans, as well as those in most other mammals, are endowed with a level of 2,3-bisphosphoglycerate (**2,3-BPG**) that is 1000 times as high as the level in all other cells and approximately matches the molar level of hemoglobin tetramer. This **metabolic intermediate** in the glycolytic pathway **binds specifically to deoxyhemoglobin** and lowers its affinity for oxygen. Thus, when hemoglobin is exposed to increasing oxygen pressure, the presence of 2,3-BPG lowers the fractional oxygen saturation, and the oxygen-binding curve is **shifted to the right**. Nearly all patients with anemia, regardless of the cause, **have elevated red-cell 2,3-BPG levels**. This adaptation greatly enhances oxygen delivery. At any given oxygen tension (measured as the partial pressure of oxygen [Po₂]), the oxygen saturation is reduced in a person with anemia. Arterial blood normally has a Po₂ of about 95 torr (or 95 mm Hg) and is nearly 100% saturated with oxygen. As red cells pass from an arteriole through its capillary bed to its vein, oxygen is released to respiring cells.

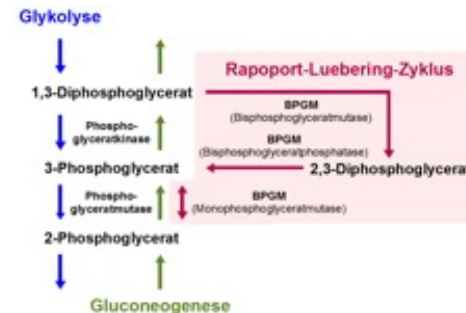


GLYCOLYSIS

HK Mangel verringert 2,3 BPG (weniger rechts Verschiebung)

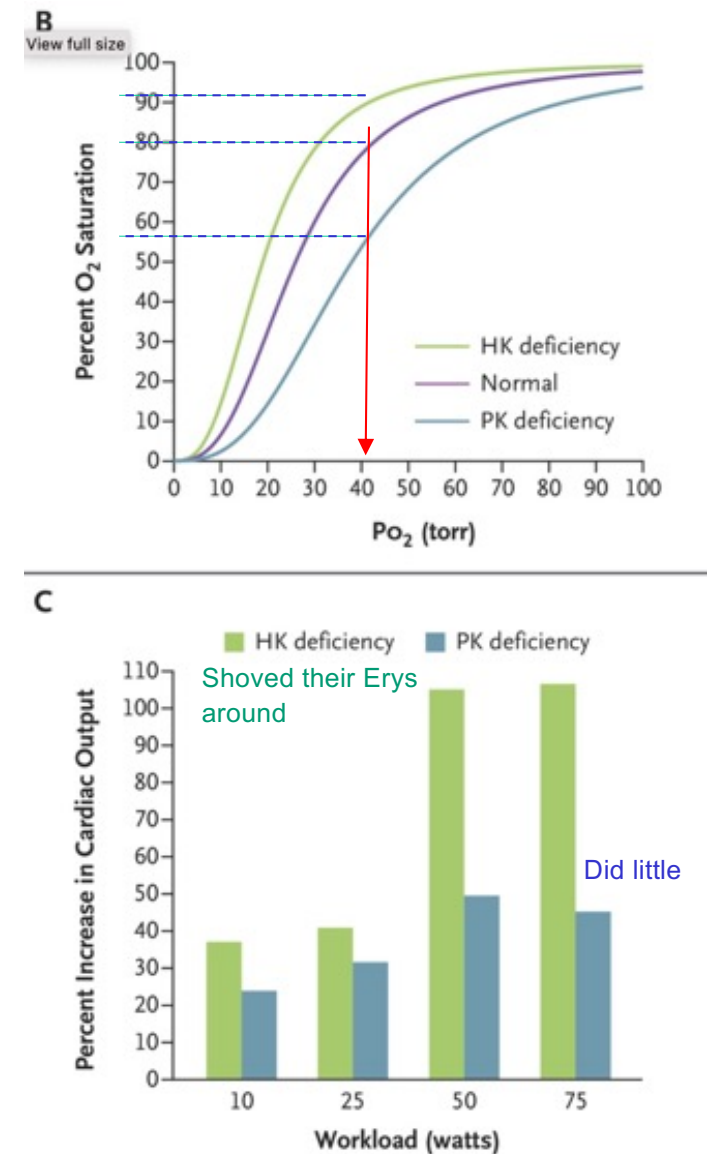


PK Mangel vermehrt 2,3 BPG (mehr rechts Verschiebung)



Differences between Hexokinase and Pyruvate Kinase Deficiencies

Some 50 years ago, Oski and his colleagues evaluated two adolescents with hemolytic anemia due to inherited defects in red-cell enzymes. One patient had a deficiency of **hexokinase**, the initial step in the glycolytic pathway mediating the phosphorylation of glucose. As a result, the **red cells were deficient in 2,3-BPG** (67% of the normal level). The red cells had increased oxygen affinity and thus **a shift to the left** in the oxygen–hemoglobin dissociation curve. The other patient had a deficiency in **pyruvate kinase**, a downstream enzyme that converts phosphoenolpyruvate to pyruvate. As a result, the red-cell **2,3-BPG level was elevated by a factor of 2.5**, which is considerably higher than the level in most other patients with anemia, with a marked **shift to the right** in the oxygen–hemoglobin dissociation curve. Although the two patients had **equivalent degrees of anemia** (hemoglobin level, approximately 10 g per deciliter), the patient with **hexokinase deficiency had dyspnea and fatigue**, whereas the patient with **pyruvate kinase deficiency was asymptomatic**. This difference in clinical presentation was in accord with measurements of cardiac output during graded exercise on a bicycle ergometer, which showed an increase in the **cardiac output by a factor of 2.5** in the patient with hexokinase deficiency, as compared with a much **more modest increase** in the patient with pyruvate kinase deficiency.

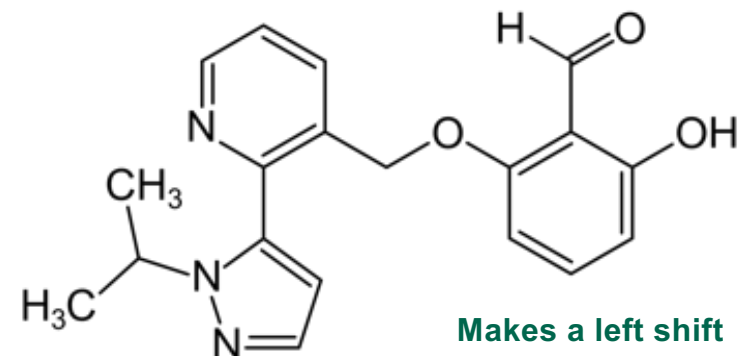
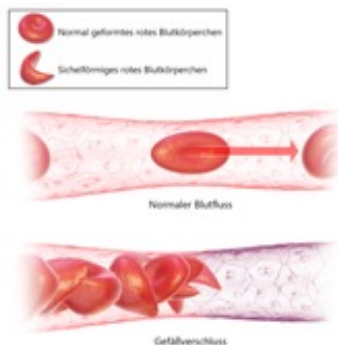


Panel B shows oxygen–hemoglobin dissociation curves for a patient with hexokinase (HK) deficiency and a patient with pyruvate kinase (PK) deficiency. Panel C shows the change in cardiac output during graded exercise in the patient with HK deficiency and the patient with PK deficiency.

Drugs Designed to Increase Hemoglobin Levels

The studies by Oski and colleagues, which showed that red-cell oxygen affinity is a major determinant of oxygen delivery, are highly relevant to the evaluation of drugs designed to increase hemoglobin levels in patients with anemia. Recently, two drugs have been introduced to increase hemoglobin levels in patients with two types of hemoglobinopathy: sickle cell disease and thalassemia.

In 2019, **voxelotor** was approved by the Food and Drug Administration (FDA) for the treatment of sickle cell disease. **Hydroxyurea** became a standard of care because of its **efficacy in reducing the frequency of vaso-occlusive crises** and in ameliorating anemia. Although **voxelotor is effective in increasing hemoglobin levels** in patients with sickle cell disease, double-blind phase 3 trials have revealed **no significant effect on the frequency or severity of vaso-occlusive events**. The drug binds covalently to the N-terminal of α -globin in oxyhemoglobin S (and F), resulting in **stabilization of a conformation of hemoglobin that cannot polymerize, as well as in a marked increase in overall oxygen affinity**. In vitro studies showed that the drug is a potent inhibitor of red-cell sickling, which **depends on the deoxygenation of hemoglobin** to form the polymerizing T conformation. The lack of efficacy of voxelotor in ameliorating vaso-occlusion is probably caused by **impaired unloading of oxygen in the microcirculation of the organs and tissues due to increased oxygen affinity**. A recent in vitro modeling study based on rigorous assessment of the effect of drugs on the kinetics of sickling under flow conditions in the microcirculation showed that **hydroxyurea enhanced oxygen delivery, whereas voxelotor did not**.

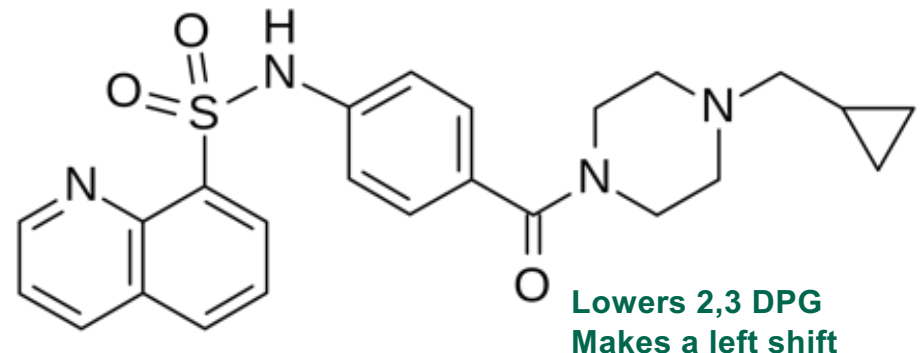


In 2022, **mitapivat** won FDA approval for the treatment of patients with hemolytic anemia due to **pyruvate kinase deficiency**. The drug, which binds to and **stabilizes the mutant enzyme**, induces an increase in hemoglobin and decreases hemolysis in these patients primarily as a result of an approximately **40% increase in red-cell ATP**. In addition, the drug causes an **approximately 35% decrease in red-cell 2,3-BPG both in these patients and in normal volunteers**. These results prompted a recent open-label phase 2 trial involving patients with either β -thalassemia or α -thalassemia who had anemia but were not dependent on transfusions, with the rationale that the ineffective erythropoiesis and hemolysis might also be mitigated by an increase in red-cell ATP. All five patients with α -thalassemia, along with 11 of the 15 patients with β -thalassemia, had an **increase in the hemoglobin level of more than 1 g per deciliter**. There was no mention in the report of changes in the red-cell 2,3-BPG level, but the **drug almost certainly caused a marked decrease**, as previously observed in unaffected persons.

In a recent phase 1 clinical trial, Xu et al. evaluated the use of **mitapivat** for the treatment of **sickle cell disease**. At the highest dose of the drug, more than half the patients had a hemoglobin response, defined as an increase in **hemoglobin of at least 1 g per deciliter**. In addition, a dose-dependent decrease in red-cell **2,3-BPG levels was observed**.

The **increase in red-cell oxygen affinity** in patients treated with either voxelotor or mitapivat would induce a **hypoxic drive** sufficient to cause the observed modest increase in hemoglobin levels, which is similar to the hemoglobin elevation in persons who have inherited a mutant hemoglobin that increases oxygen affinity.

Mitapivat ist ein Pyruvatkinase-Aktivator, der allosterisch an das Pyruvatkinase-Tetramer bindet und die Aktivität der Pyruvatkinase (PK) erhöht.



Conclusions

These scenarios about treatment with **voxelotor or mitapivat** should alert physicians to be aware that at a given hemoglobin level, drug-induced alterations in the **oxygen-binding curve** can have an impressive effect on oxygen delivery, similar to that observed by Oski and his colleagues in the two adolescents with red-cell enzyme deficiencies. **Medical students are properly taught that the signs and symptoms of anemia are due to an insufficient supply of oxygen to organs and tissues.** Practicing physicians use the blood hemoglobin level as a readily measured and accurate assessment of the severity of anemia and its response to therapy. However, in evaluating the effect of drugs designed to alleviate anemia, therapy-induced increases in the hemoglobin level may be misleading, even illusory. **It is important to be aware that the drug may have an adverse effect on oxygen delivery that offsets its enhancement of oxygen-carrying capacity.**

The development of new drugs imposes a large financial burden on our health care system and arouses hope on the part of the patients for whom they are prescribed. An accurate assessment of the efficacy and value of a drug often depends on a firm understanding of the underlying physiology.

A 31-Year-Old Woman with Postpartum Abdominal Pain and Fever

A 31-year-old woman was admitted to this hospital 15 days after the birth of her first child because of **abdominal pain and fever**.

The patient had received routine prenatal care at this hospital. Serologic screening during the pregnancy showed immunity to rubella. Rectovaginal culture was positive for group B streptococcus. Tests for syphilis, hepatitis B virus surface antigen, gonorrhea, chlamydia, and human immunodeficiency virus were negative.

Sixteen days before this admission, the patient went into labor at 38 weeks 1 day of gestation. She was admitted to this hospital. The white-cell count was 13,800 per microliter (reference range, 4500 to 11,000), and the hemoglobin level was 14.0 g per deciliter (reference range, 12.0 to 16.0); treatment with intravenous penicillin was started. Artificial rupture of the membranes revealed clear, odorless fluid, and infusion of oxytocin was started. Six hours after artificial rupture of the membranes, the patient gave birth to a healthy baby by vaginal delivery. Three minutes later, the placenta was delivered intact. Immediately after delivery, hemorrhage due to uterine atony occurred; there was an estimated blood loss of 500 ml. The patient began breast-feeding, and on postpartum day 1, she was discharged.

Six days before the current admission, on postpartum day 9, pain in the **left upper quadrant** developed. The pain was dull, radiated to the left flank and back, and was worse with movement and deep breathing. The patient presented to a local urgent care clinic; **urine was obtained for culture, and empirical treatment with amoxicillin–clavulanate was started**.

Five days before this admission, on postpartum day 10, abdominal pain persisted, and a fever with a temporal temperature of 38.3° C developed. The patient sought evaluation in the emergency department of this hospital. **She rated the abdominal pain at 10** on a scale of 0 to 10. A review of systems was notable for nausea and minimal lochia; there was no diarrhea, constipation, dysuria, hematuria, or breast tenderness.

Variable	Reference Range, Adults, This Hospital†	Previous Admission, Postpartum Day 10	This Admission, Postpartum Day 15
Blood			
Sodium (mmol/liter)	135–145	138	142
Potassium (mmol/liter)	3.4–5.0	3.5	3.9
Chloride (mmol/liter)	98–108	103	105
Carbon dioxide (mmol/liter)	23–32	21	26
Urea nitrogen (mg/dl)	8–25	8	8
Creatinine (mg/dl)	0.60–1.50	0.56	0.56
Glucose (mg/dl)	74–106	132	98
Lactic acid (mmol/liter)	0.5–2.0	1.6	0.9
Alanine aminotransferase (U/liter)	7–33	—	153
Aspartate aminotransferase (U/liter)	9–32	—	44
Alkaline phosphatase (U/liter)	30–100	—	194
Total bilirubin (mg/dl)	0.0–1.0	—	0.3
White-cell count (per μ l)	4500–11,000	20,700	10,330
Differential count (per μ l)			
Neutrophils	1800–7700	17,190	7470
Lymphocytes	1000–4800	1850	1630
Monocytes	200–1200	1360	770
Eosinophils	0–900	30	250
Basophils	0–300	10	80
Hemoglobin (g/dl)	12.0–16.0	11.4	11.2
Hematocrit (%)	36.0–46.0	34.9	34.0
Platelet count (per μ l)	150,000–400,000	218,000	392,000
Urine			
Bilirubin	Negative	Negative	Negative
Urobilinogen	Negative	1+	Negative
Blood	Negative	2+	2+
Glucose	Negative	Negative	Negative
Ketones	Negative	Trace	Negative
Leukocyte esterase	Negative	2+	1+
Nitrites	Negative	Negative	Negative
Red cells (per high-power field)	0–2	10–20	10–20
White cells (per high-power field)	<10	20–50	<10

The patient had not been pregnant before the recent pregnancy; before this pregnancy, **she had taken oral contraceptives for 12 years.**

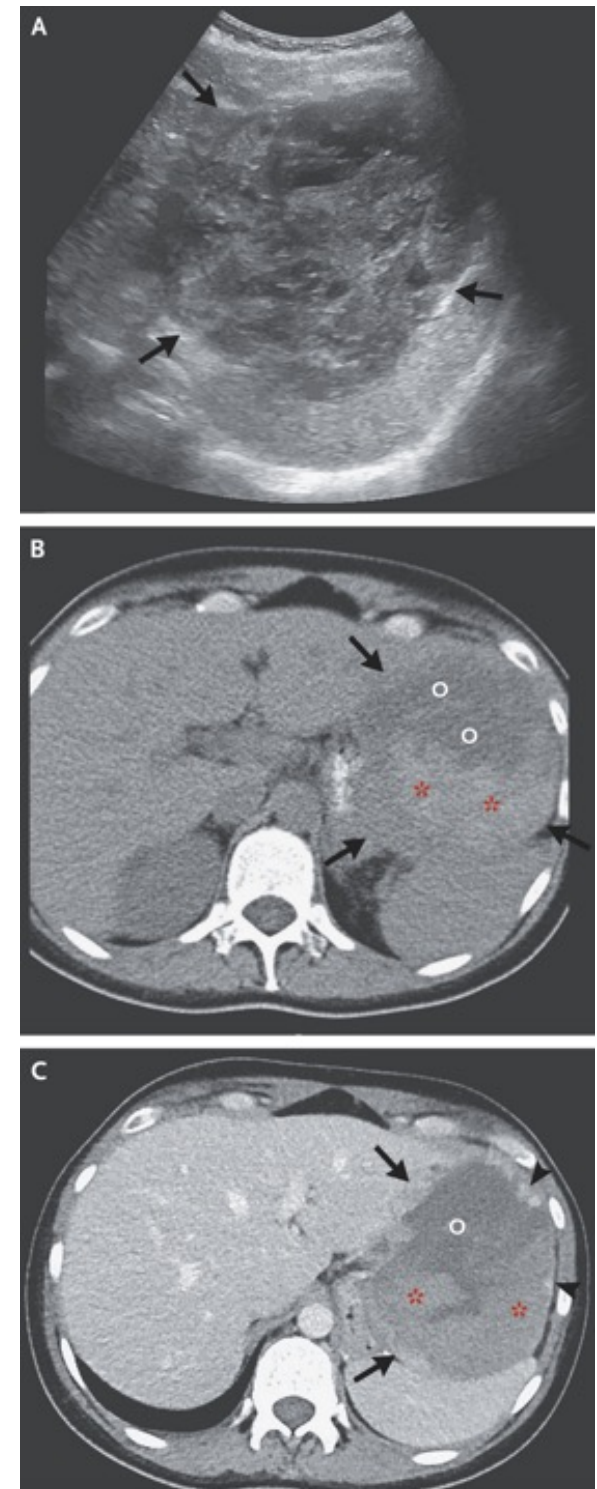
Treatment with ceftriaxone was started, and the patient was admitted to the hospital for presumed pyelonephritis. On hospital day 3, when the fever and abdominal pain resolved, the patient was discharged home to complete a course of amoxicillin.

Urobilinogen ist ein Abbauprodukt von Bilirubin und zählt damit zu den Gallenfarbstoffen (Bilane). Es wird bakteriell aus Bilirubin gebildet, das aus der Gallenblase in den Darm abgegeben wird. 20 % des Urobilinogens werden rückresorbiert, über die Pfortader der Leber zugeführt, weiter abgebaut und auch teilweise über den Urin ausgeschieden. Die normale Urobilinogenkonzentration im Urin reicht von 0,1–1,8 mg/dl (1,7–30 μ mol/l), Konzentrationen > 2,0 mg/dl (34 μ mol/l) gelten als pathologisch.

- hämolytischer **Anämie** (vermehrter Abbau roter Blutkörperchen)
- **Verstopfung, Darmentzündung**
- Infektionen der Gallenwege
- akute und chronische **Leberentzündung**
- toxischen Leberschäden, **Lebertumoren**
- Stauungsleber (bei **Herzinsuffizienz**)

After the patient presented for the third time with these symptoms, on postpartum day 15, CT of the abdomen and pelvis was performed; a heterogeneous mass with mixed attenuation was identified in the left lobe of the liver. The white-cell count was 10,330 per microliter on readmission — a decrease from a level of 20,700 per microliter obtained 5 days earlier. This decrease in white-cell count may have been the result of partial treatment of a superimposed urinary tract infection. The hemoglobin level was 11.2 g per deciliter on admission on postpartum day 15 but decreased to 9.7 g per deciliter on repeat testing, a finding that was thought to indicate hemorrhage into the liver mass, given the increased abdominal pain and no other identified source of bleeding.

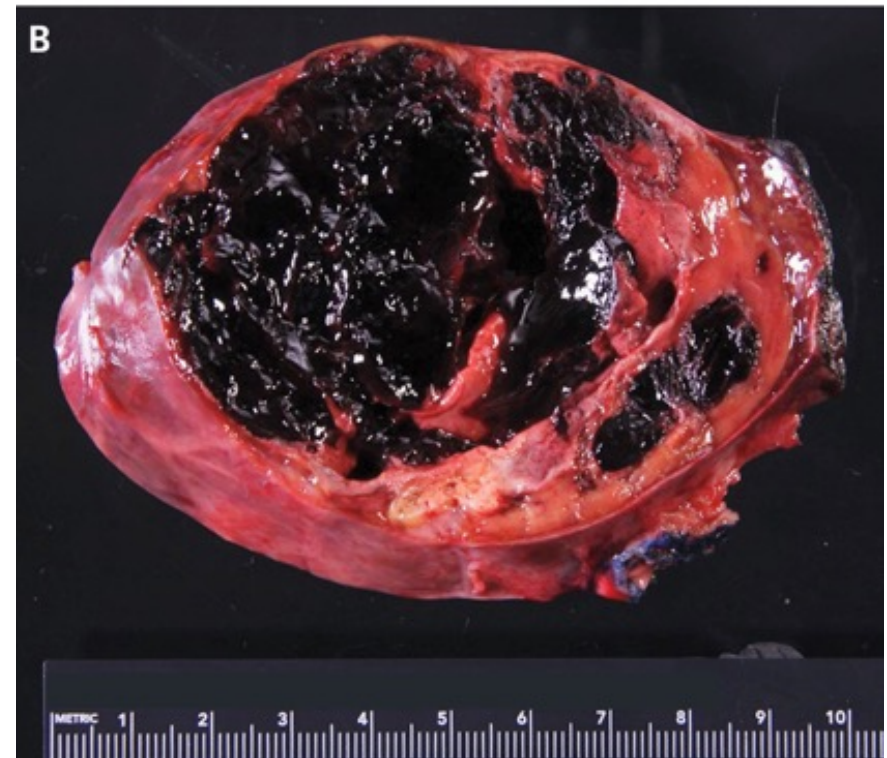
A transverse ultrasound image of the left lobe of the liver (Panel A) shows a large exophytic, heterogeneous lesion (arrows). CT images obtained before (Panel B) and after (Panel C) the administration of oral and intravenous contrast material confirm a large exophytic mass (arrows) arising from the left hepatic lobe and exerting mass effect on the stomach. The mass contains spontaneously hyperdense material that does not enhance after administration of the contrast material (asterisks) and is consistent with hematoma, a large nonenhancing component that is most likely necrotic (circles), and some vividly enhancing peripheral components (arrowheads).



Hepatic-Resection Specimen for Gross Examination.

The hepatic capsular surface was smooth and dull. Sectioning of the specimen revealed a 15.9-cm mass that was predominantly hemorrhagic with a tan-to-yellow, soft, centrally necrotic cut surface; the mass was located 0.2 cm from the transected margin of the liver and 0.3 cm from the diaphragmatic margin. Fifty percent of the mass was hemorrhagic and approximately 30% was necrotic, with possible viable tumor along the periphery of the specimen.

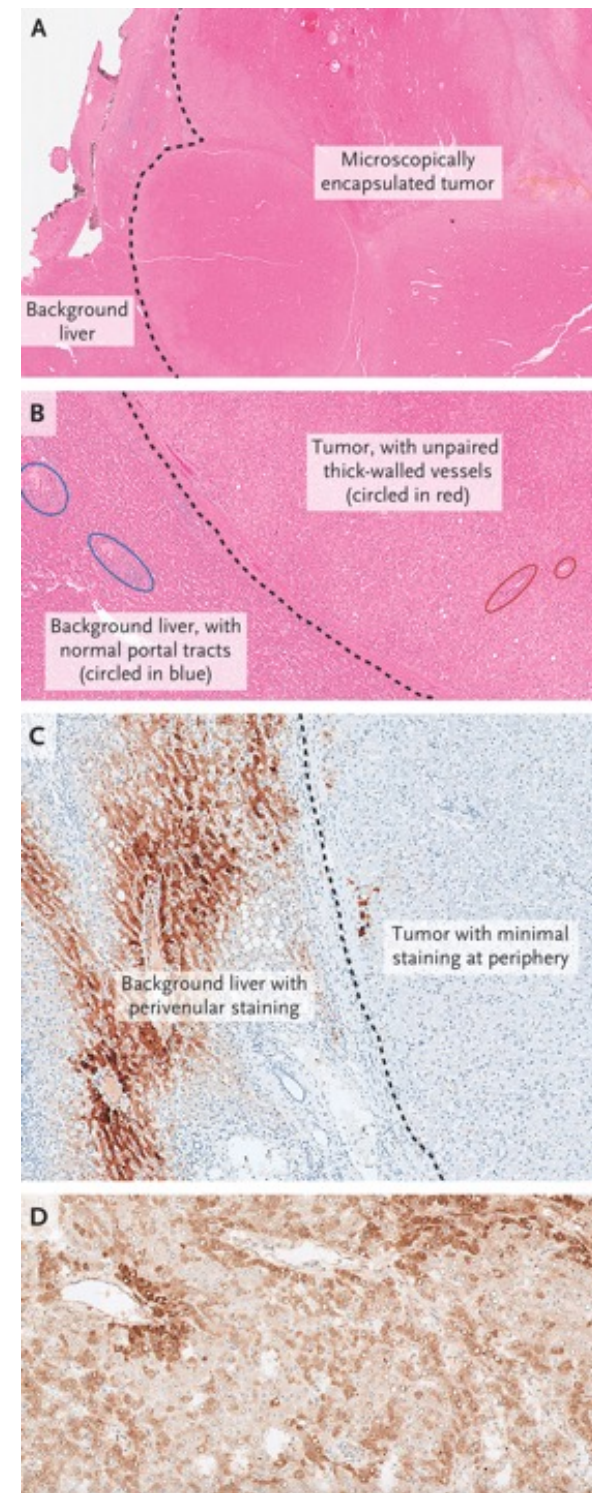
On gross examination, the solitary resected mass measures 15.9 cm in length, is hemorrhagic, and is found to be confined to the liver (Panel A). The cut surface is tan-to-yellow, soft, and centrally necrotic (Panel B).



Hepatic-Resection Specimen for Microscopic Examination.

On microscopic examination, hematoxylin and eosin staining shows a benign, microscopically encapsulated hepatic tumor (Panel A). Numerous unpaired thick-walled vessels are identified in the tumor (Panel B). The hepatic trabeculae are noted to be 1 to 2 cells thick. Immunostains show very focal tumor-cell positivity for glutamine synthetase (Panel C) and patchy staining with serum amyloid A (Panel D).

The patient was seen in the clinic at 8 weeks postpartum. She reported no abdominal pain or other symptoms. Because estrogen-containing contraception was contraindicated given the diagnosis of hepatic adenoma, an etonogestrel (progesterone-only) implant was placed for postpartum contraception. The patient continued to have mildly elevated liver-function test results; the ALT level was 48 U per liter and the AST level 33 U per liter. The general surgery service recommended performing repeat magnetic resonance imaging or CT if the patient becomes symptomatic, and the obstetrics service recommended resection of any larger adenoma (i.e., a lesion >5 cm) before any subsequent pregnancy.



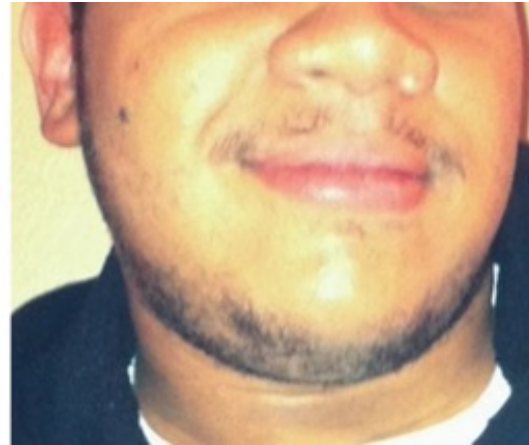
MPXV Transmission at a Tattoo Parlor

From July 6 to 19, 2022, a total of **21 persons** were infected by monkeypox (recently renamed mpox) virus (MPXV) that was likely to have been transmitted by means of piercing or tattooing at the same parlor in Cadiz, Spain. Of the 21 infected patients, **14 (67%) were female** and 9 (43%) were younger than 18 years of age. The median age of the patients was 26 years (interquartile range, 16 to 38). The patients had no history of recent high-risk sexual activity (e.g., sex without a barrier method of contraception or with multiple partners), travel to areas where mpox is endemic, or close contact with MPXV-infected persons.



Cutaneous necrosis at the area of the piercing or tattoo and surrounding umbilicated pustules with an underlying edematous and erythematous plaque are seen in photographs of patients who had undergone piercing or tattooing and become infected with the mpox virus (MPXV) (Panels A through D).

Papulopustules appeared in clusters, sometimes with scalloped edges reminiscent of herpesvirus infections. However, unlike herpes lesions, these pustules were solid in content (pseudopustules). Panel E shows skin-disseminated lesions of scattered erythematous papules and nonclustered umbilicated pustules over erythematous macules. Disseminated lesions, which are usually described as monomorphic, may appear in different evolutionary stages, giving a “starry sky” appearance. Panel F shows more detail of a nonclustered umbilicated pustule over an erythematous macule.



A 34-year-old man was admitted to the hospital with diabetic ketoacidosis. He reported having had blurry vision, increasing shoe size, and a change in his facial features over the past several years. On exam, he was found to have bitemporal hemianopsia. Which of the following is the most likely cause of his presentation?

Anabolic steroid use

Beckwith–Wiedemann syndrome

Nelson's syndrome

Pachydermoperiostosis

Somatotropic pituitary adenoma



The correct answer is somatotropic pituitary adenoma. Laboratory studies showed elevated levels of insulin-like growth factor 1 and growth hormone, confirming a diagnosis of acromegaly. Magnetic resonance imaging of the head revealed a pituitary macroadenoma, which was then resected and found on pathology to stain positive for growth hormone. He was treated with octreotide and required a second resection 8 months after the initial surgery.

Das Beckwith-Wiedemann-Syndrom, kurz BWS, ist eine genetisch bedingte Wachstumsstörung, die zu den Großwuchs-Syndromen zählt. Sie zeichnet sich bereits intrauterin durch ein unbalanciertes Wachstum der verschiedenen Organe aus. Ursächlich für das Auftreten des Beckwith-Wiedemann-Syndroms sind mehrere genetische Defekte auf Chromosom 11 (p11-15). Hierbei wurde in Forschungsarbeiten Mikrodeletionen, Hypermethylierungen und eine uniparentale Disomie 11 (paternal) festgestellt, die zu einem Verlust von aktiven Genen führen. Diese Veränderungen führen schließlich zu einem Defekt des IGF-2-, CDKN1C- und H19-Gens.

Beim Nelson-Syndrom handelt es sich um ein reaktives, starkes Wachstum der Hypophyse, speziell der basophilen kortikotropen Zellen, nach einer bilateralen Entfernung der Nebennieren (Adrenalektomie), z.B. bei Morbus Cushing. Es ist somit die Reaktion auf eine iatrogene Nebenniereninsuffizienz.

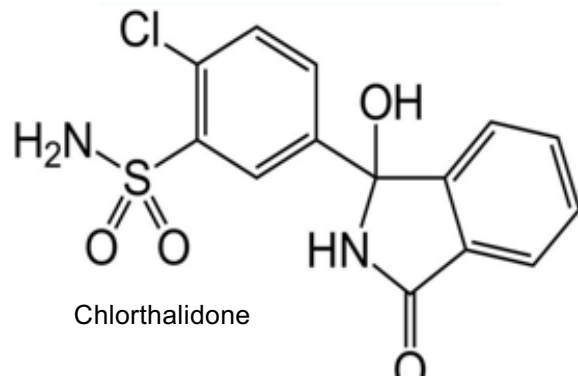
Chlortalidon ist chemisch gesehen ein Sulfonamid und zählt zu den Thiazid-Diuretika. Chlortalidon inhibiert im distalen Tubulus-System der Niere den Natriumchlorid-Kanal, sodass weder Natrium noch Chlorid rückresorbiert werden können. So verbleiben diese osmotisch wirksamen Ionen im Tubulus und führen dazu, dass auch Wasser, welches normalerweise den Ionen folgt, nicht rückresorbiert wird. Folglich wird dieses samt Natrium und Chlorid ausgeschieden, was mit einer Entwässerung einhergeht.

Chlortalidon hat zwei Vorteile: **Erstens** ist es in großen Studien an Tausenden von Patienten mit Erfolg getestet worden. Das umfasst die größten und wichtigsten unabhängig durchgeführten Blutdruckstudien wie ALLHAT und SPRINT. Dagegen ist HCT nur in kleineren Studien untersucht worden.

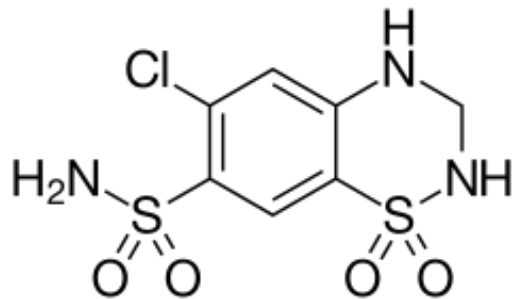
Wenn man viele Studien zusammenfasst, senkt Chlortalidon gegenüber HCT das relative Risiko für Herz-Kreislauf-Komplikationen um 21 % (Roush GC et al., Hypertension 2012). Dennoch wird HCT in Deutschland aus Tradition bzw. Gewohnheit viel häufiger verwendet als Chlortalidon, was man durchaus kritisch sehen kann.

Wirkung von Chlortalidon gleichmäßiger

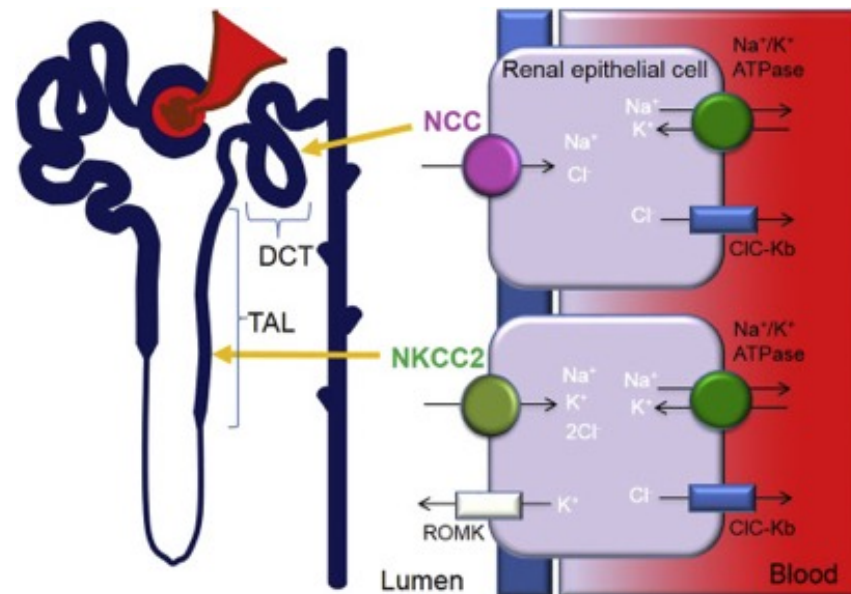
Zweitens hat Chlortalidon eine deutlich längere Halbwertszeit im Körper. Das heißt, dass die Wirkung länger anhält und gleichmäßiger ist als die von HCT. Damit „verzeiht“ Chlortalidon auch mal das gelegentliche Vergessen einer Tabletteneinnahme.



Chlortalidone



Hydrochlorthiazide

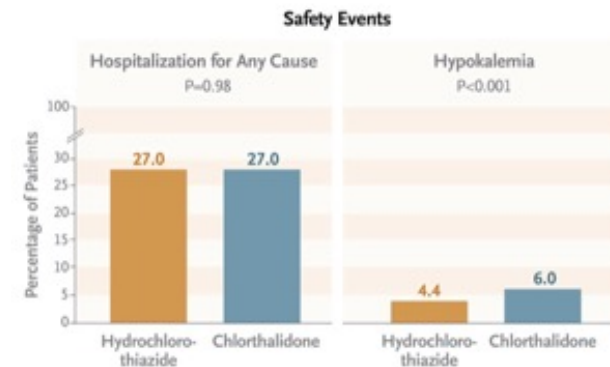
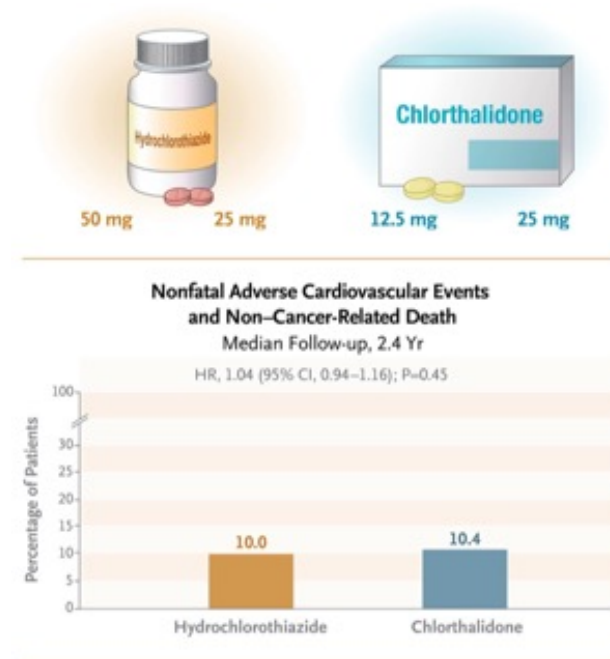


Chlorthalidone vs. Hydrochlorothiazide for Hypertension—Cardiovascular Events

Whether chlorthalidone is superior to hydrochlorothiazide for preventing major adverse cardiovascular events in patients with hypertension is unclear. In a pragmatic trial, we randomly assigned adults 65 years of age or older who were patients in the Department of Veterans Affairs health system and had been receiving hydrochlorothiazide at a daily dose of 25 or 50 mg to continue therapy with hydrochlorothiazide or to switch to chlorthalidone at a daily dose of 12.5 or 25 mg. The primary outcome was a composite of nonfatal myocardial infarction, stroke, heart failure resulting in hospitalization, urgent coronary revascularization for unstable angina, and non-cancer-related death. Safety was also assessed.

LIMITATIONS AND REMAINING QUESTIONS

- More patients assigned to receive chlorthalidone switched back to hydrochlorothiazide, as compared with patients assigned to continue treatment with hydrochlorothiazide switching over to chlorthalidone — possibly owing to the open-label nature of the trial.
- Only 5% of participants were receiving a daily 50-mg dose of hydrochlorothiazide at baseline; thus, the trial primarily compared hydrochlorothiazide at a daily dose of 25 mg with chlorthalidone at a daily dose of 12.5 mg, and the results should not be extrapolated to other dosages.



CONCLUSIONS

In a large pragmatic trial among U.S. veterans with hypertension, patients who received chlorthalidone did not have a lower occurrence of nonfatal cardiovascular events or non-cancer-related death than those who received hydrochlorothiazide.

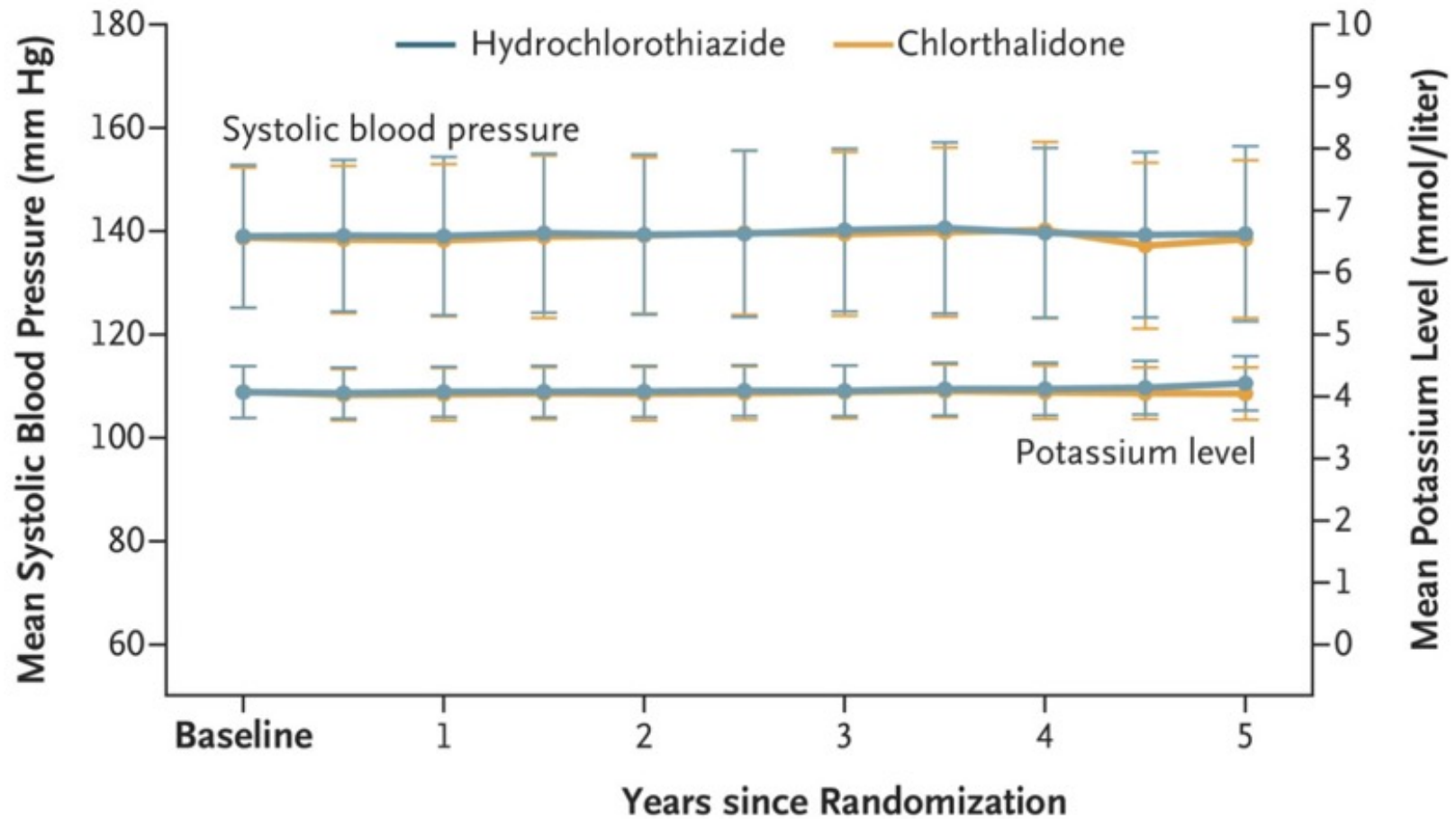
The Diuretic Comparison Project aimed to evaluate whether chlorthalidone, as compared with hydrochlorothiazide, would reduce the risk of major nonfatal cardiovascular disease outcomes and non-cancer-related deaths in older patients with hypertension who were receiving hydrochlorothiazide at baseline. After informed consent was obtained, the patient's provider was sent an electronic order to sign if the provider assented to the patient undergoing randomization. Patients were randomly assigned to continue receiving hydrochlorothiazide or to switch to chlorthalidone. If a provider declined to assent to a patient undergoing randomization, the patient was notified of the decision and the patient's data were not included in the trial.

Patients who were assigned to the hydrochlorothiazide group continued to receive the medication according to their current prescription. Patients who were assigned to switch to chlorthalidone were assigned medication orders prescribing chlorthalidone and discontinuing hydrochlorothiazide; the orders were placed in the EHR and sent to the patient's provider for electronic signature. Patients in the chlorthalidone group for whom hydrochlorothiazide had been prescribed at a daily dose of 25 or 50 mg were switched to receive chlorthalidone at a daily dose of 12.5 or 25 mg, respectively. All the patients who underwent randomization were included in the intention-to-treat analysis. Patients and providers were aware of the group assignments.

Characteristic	Chlorthalidone (N = 6756)	Hydrochlorothiazide (N = 6767)
Age — yr	72.4±5.4	72.5±5.3
Male sex — no. (%)	6536 (96.7)	6556 (96.9)
Race or ethnic group — no. (%)†		
Black	1004 (14.9)	1023 (15.1)
White	5229 (77.4)	5225 (77.2)
Other	523 (7.7)	519 (7.7)
Not Hispanic or Latino	6281 (93.0)	6268 (92.6)
Resided in rural area — no. (%)‡	3043 (45.0)	3079 (45.5)
Body-mass index§	31.7±5.8	31.8±5.9
Medical history — no. (%)		
Diabetes	2967 (43.9)	3062 (45.2)
Heart failure	525 (7.8)	526 (7.8)
MI	230 (3.4)	258 (3.8)
Stroke	534 (7.9)	495 (7.3)
MI and stroke¶	733 (10.8)	722 (10.7)
Estimated GFR <60 ml/min/1.73 m ² — no. (%)	1550 (22.9)	1547 (22.9)
Current smoker — no. (%)	1520 (22.5)	1437 (21.2)
Receiving hydrochlorothiazide at a daily dose of 25 mg — no. (%)	6379 (94.4)	6402 (94.6)
Systolic blood pressure — mm Hg	139±14	139±14
No. of antihypertensive drugs prescribed	2.6±1.0	2.6±1.1
Antihypertensive medications — no. (%)		
Hydrochlorothiazide alone	889 (13.2)	866 (12.8)
Hydrochlorothiazide plus one additional blood-pressure medication	2352 (34.8)	2284 (33.8)
Hydrochlorothiazide plus two additional blood-pressure medications	2180 (32.3)	2221 (32.8)
Hydrochlorothiazide plus three additional blood-pressure medications	1061 (15.7)	1090 (16.1)
Hydrochlorothiazide plus four additional blood-pressure medications	274 (4.1)	306 (4.5)

Systolic Blood Pressure, Potassium Level, and Potassium Supplementation over Time.

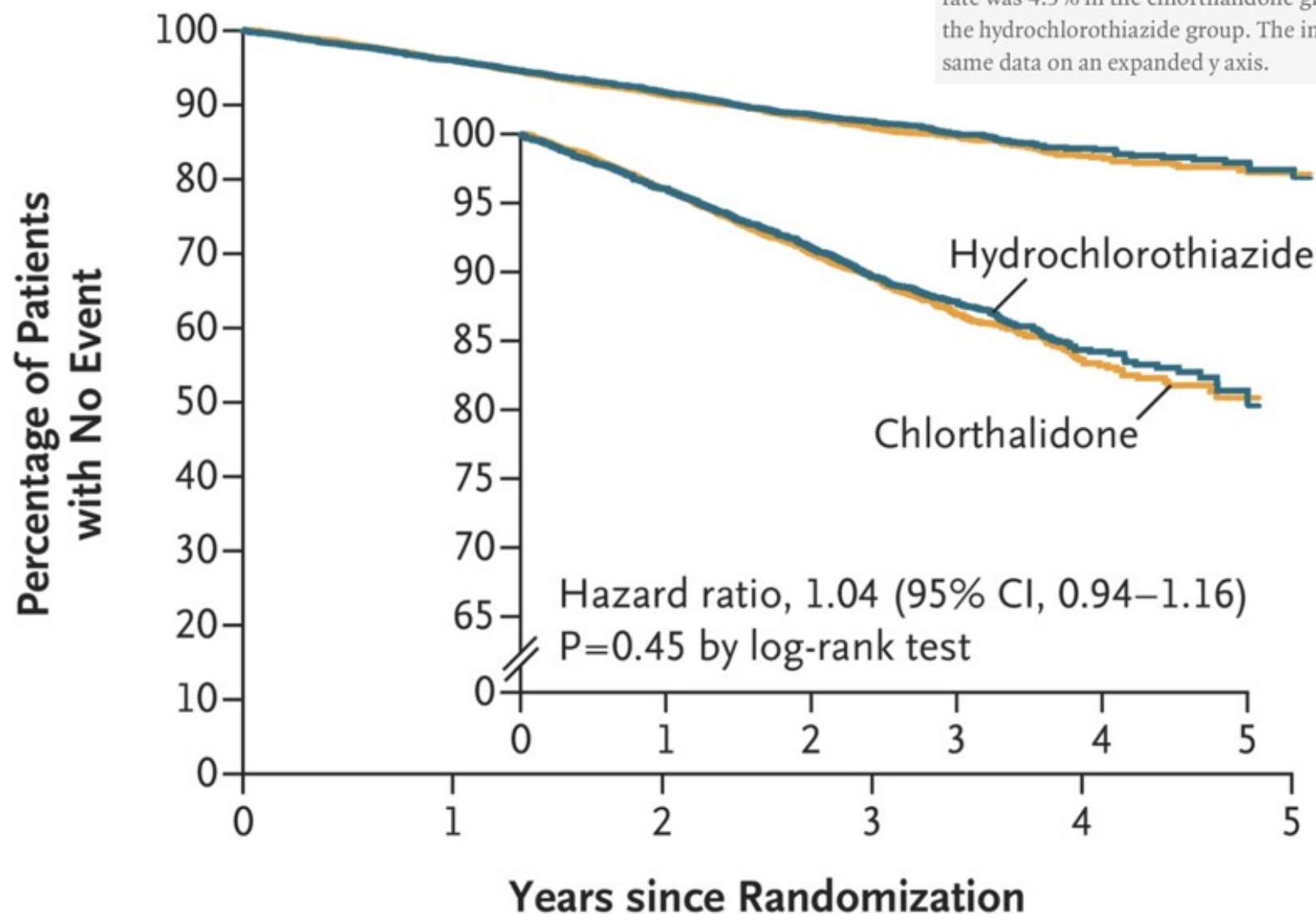
Laboratory values for potassium include both serum and plasma measurements. I bars indicate confidence intervals.



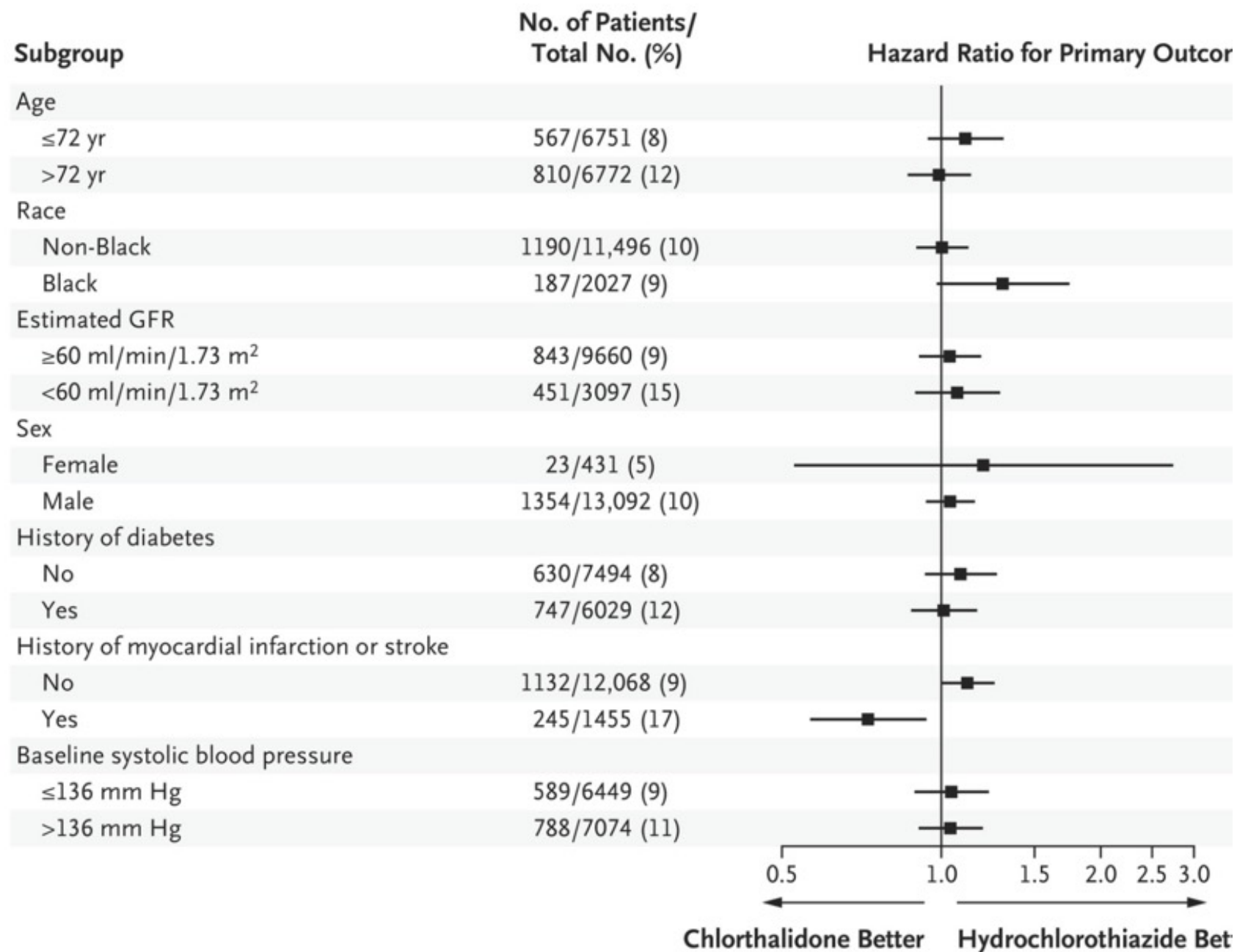
Primary, Secondary, and Safety Outcomes.

Outcome	Chlorthalidone (N = 6756)	Hydrochlorothiazide (N = 6767)	Hazard Ratio (95% CI) [†]
Primary composite outcome — no. (%) [‡]	702 (10.4)	675 (10.0)	1.04 (0.94–1.16) [§]
Secondary outcomes: components of the primary outcome — no. (%)			
MI	142 (2.1)	140 (2.1)	1.02 (0.80–1.28)
Stroke	83 (1.2)	83 (1.2)	1.00 (0.74–1.36)
Hospitalization due to heart failure	242 (3.6)	232 (3.4)	1.04 (0.87–1.25)
Unstable angina leading to urgent coronary re-vascularization	20 (0.3)	13 (0.2)	1.54 (0.77–3.10)
Non–cancer-related death	359 (5.3)	354 (5.2)	1.01 (0.88–1.17)
Death from any cause — no. (%)	446 (6.6)	448 (6.6)	1.00 (0.87–1.13)
Expected adverse events — no. (%)			
New allergic or adverse reaction to thiazide-type diuretic	109 (1.6)	21 (0.3)	5.23 (3.28–8.35)
Hypokalemia	406 (6.0)	298 (4.4)	1.38 (1.19–1.60)
As primary cause of hospitalization	98 (1.5)	73 (1.1)	1.35 (1.00–1.82)
Potassium level <3.1 mmol/liter	335 (5.0)	243 (3.6)	1.39 (1.18–1.64)
Hospitalization for acute kidney injury	495 (7.3)	512 (7.6)	0.95 (0.85–1.09)

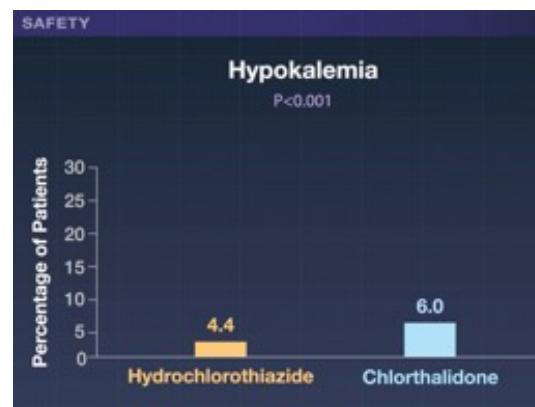
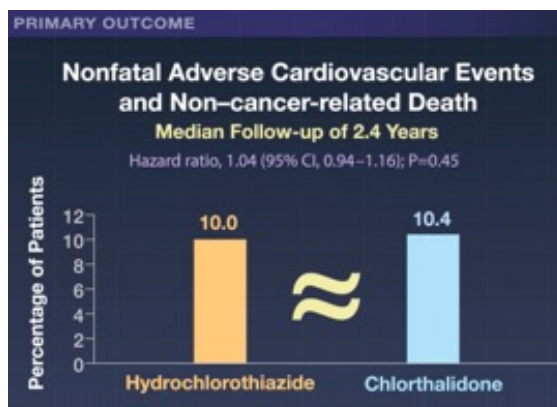
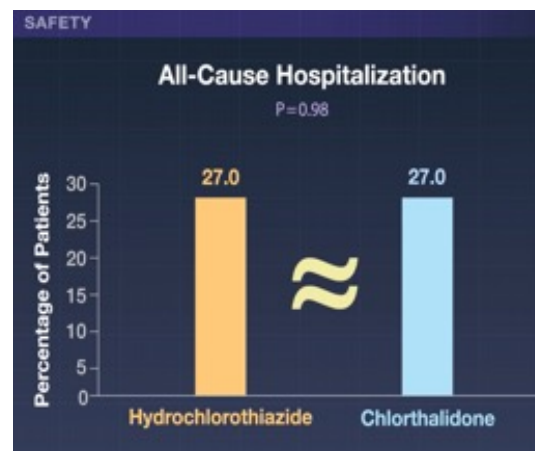
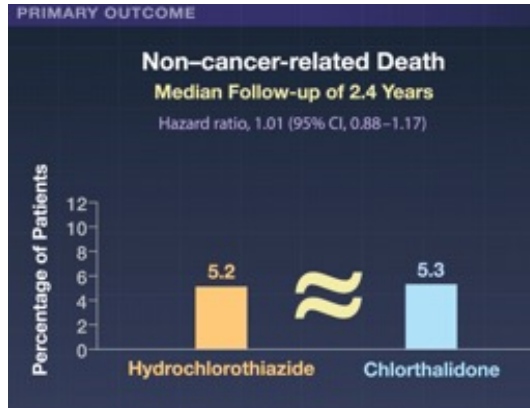
Kaplan–Meier Survival Curve for the Primary Outcome.



A primary composite outcome event (a composite of nonfatal myocardial infarction, stroke, heart failure that resulted in hospitalization, urgent coronary revascularization for unstable angina, and non–cancer-related death) occurred in 1377 patients: 702 (10.4%) in the chlorthalidone group and 675 (10.0%) in the hydrochlorothiazide group. The observed annual event rate was 4.5% in the chlorthalidone group and 4.3% in the hydrochlorothiazide group. The inset shows the same data on an expanded y axis.



Thiazide Diuretics



The dose levels of the two diuretics were also an important limitation of this pragmatic trial. Previous trials that showed the benefits of these medications on cardiovascular outcomes used higher target doses (≥50 mg of hydrochlorothiazide or ≥25 mg of chlorthalidone). However, most patients currently treated with hydrochlorothiazide, including the VA population, receive 12.5 to 25 mg, and only 5% of the patients in this trial had been receiving 50 mg of hydrochlorothiazide at baseline. Therefore, the primary comparison in this trial was between 25 mg of hydrochlorothiazide and 12.5 mg of chlorthalidone. These results should not be extrapolated to other doses of these medications.

Der umgangssprachliche Begriff Ebola kann verschiedene Bedeutungen haben:

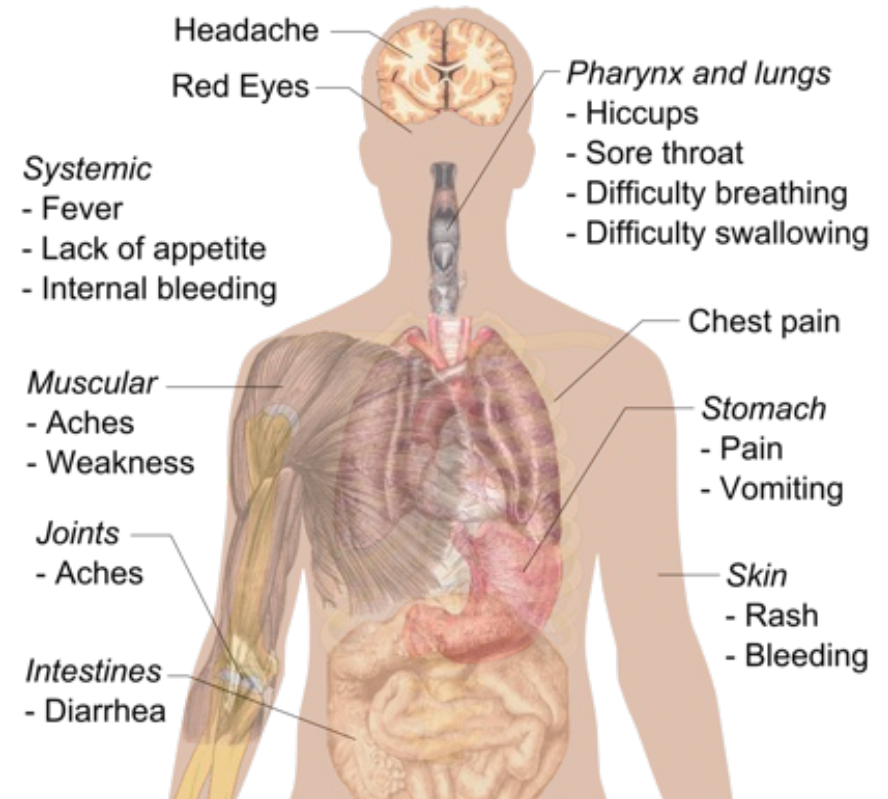
Das Ebolafieber ist eine häufig tödlich verlaufende Infektionskrankheit, die mit hämorrhagischem Fieber einhergehen kann und durch das Ebolavirus ausgelöst wird.

Das Ebolavirus, früher auch Zaire-Ebolavirus genannt, ist eines von 5 bekannten Viren aus der Gattung der Ebolaviren und der Familie der Filoviren. Das Ebolavirus ist der Auslöser der bislang (2020) größten Ebolafieber-Epidemie.

Wo wurde Ebola entdeckt?



Symptoms of Ebola



Headache

Red Eyes

Pharynx and lungs

- Hiccups

- Sore throat

- Difficulty breathing

- Difficulty swallowing

Systemic

- Fever

- Lack of appetite

- Internal bleeding

Muscular

- Aches

- Weakness

Joints

- Aches

Intestines

- Diarrhea

Chest pain

Stomach

- Pain

- Vomiting

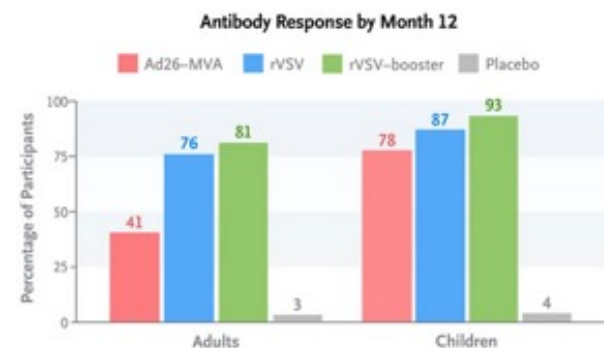
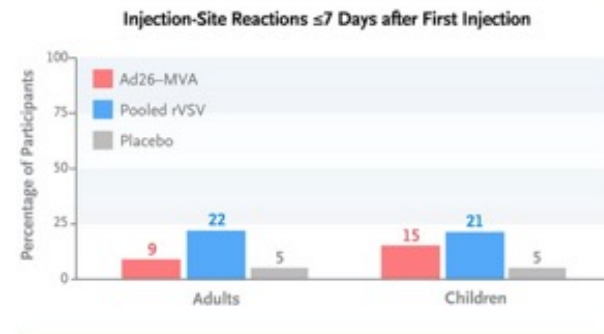
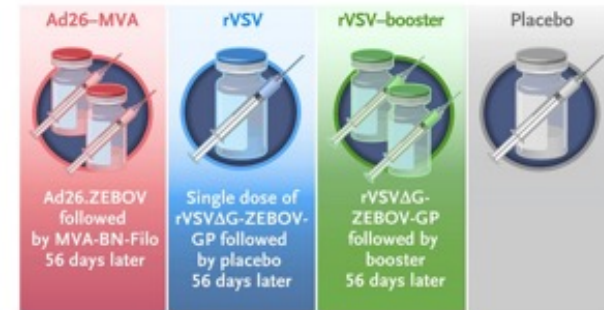
Skin

- Rash

- Bleeding

Randomized Trial of Vaccines for Zaire Ebola Virus Disease

Questions remain concerning the rapidity of immune responses and the durability and safety of vaccines used to prevent Zaire Ebola virus disease. We conducted two randomized, placebo-controlled trials — one involving adults and one involving children — to evaluate the safety and immune responses of three vaccine regimens against Zaire Ebola virus disease: Ad26.ZEBOV followed by MVA-BN-Filo 56 days later (the Ad26–MVA group), rVSVΔG-ZEBOV-GP followed by placebo 56 days later (the rVSV group), and rVSVΔG-ZEBOV-GP followed by rVSVΔG-ZEBOV-GP 56 days later (the rVSV–booster group). The primary end point was antibody response at 12 months, defined as having both a 12-month antibody concentration of at least 200 enzyme-linked immunosorbent assay units (EU) per milliliter and an increase from baseline in the antibody concentration by at least a factor of 4.



CONCLUSIONS

In two clinical trials involving children and adults, all three vaccine regimens elicited immune responses by day 14 that continued through month 12 and presented no safety concerns.

Follow-up

Follow-up visits occurred on days 7, 14, and 28 after the first dose of vaccine or placebo. The second or booster dose of vaccine or placebo was administered on day 56, with further follow-up visits at day 63 and during months 3, 6, and 12. Antibody response was assessed at each follow-up visit, injection-site reactions and symptoms (e.g., feverishness and headache) were assessed through month 6, and data on serious adverse events were collected through month 12.

Antibody Responses to Ebola Glycoprotein

Serum concentrations of IgG binding antibodies against the Ebola virus surface glycoprotein were measured at baseline and at each follow-up visit with the Filovirus Animal Nonclinical Group (FANG) enzyme-linked immunosorbent assay (ELISA) (Section S3.6.1 and the protocol). The primary immunogenicity end point was an antibody response at month 12, with response defined as an antibody concentration of at least 200 ELISA units (EU) per milliliter and an increase from baseline in the antibody concentration by at least a factor of 4. As in other studies, including the Partnership for Research on Ebola Virus in Liberia (PREVAIL) I trial, an increase from baseline in the antibody concentration by at least a factor of 4 was used to define antibody response. An antibody concentration of at least 200 EU per milliliter and an increase from baseline by at least a factor of 2 were included because it was considered a possible correlate of protection. As a secondary objective, we compared the rVSV Δ G-ZEBOV-GP and Ad26.ZEBOV–MVA-BN-Filo regimens, separately, with placebo in an analysis of immediacy of response at day 14. The protocol also specified primary objectives in support of regulatory submissions by Merck Sharp and Dohme and Janssen. These objectives stated that the time point of the antibody comparison with placebo for the rVSV Δ G-ZEBOV-GP vaccine (Merck Sharp and Dohme) would be day 28 and the time point for the Ad26.ZEBOV–MVA-BN-Filo regimen (Janssen) would be month 3. Antibody concentrations were determined in two laboratories.

Characteristic	Ad26-MVA Group	rVSV Group	rVSV-Booster Group	Placebo Group	Total
Adults					
No. of participants	396	395	197	412	1400
Age					
Median (IQR) — yr	27 (21–40)	27 (20–39)	26 (20–35)	27 (20–38)	27 (20–38)
Distribution — no. (%)					
18–29 yr	227 (57)	213 (54)	119 (60)	238 (58)	797 (57)
30–39 yr	67 (17)	89 (23)	41 (21)	84 (20)	281 (20)
≥40 yr	102 (26)	93 (24)	37 (19)	90 (22)	322 (23)
Female sex — no. (%)	171 (43)	182 (46)	87 (44)	187 (45)	627 (45)
Country — no. (%)					
Guinea	121 (31)	130 (33)	66 (34)	135 (33)	452 (32)
Liberia	73 (18)	70 (18)	35 (18)	81 (20)	259 (18)
Mali	81 (20)	84 (21)	41 (21)	86 (21)	292 (21)
Sierra Leone	121 (31)	111 (28)	55 (28)	110 (27)	397 (28)
HIV-positive status — no. (%)	6 (2)	13 (3)	2 (1)	4 (1)	25 (2)
Ebola IgG concentration†					
≥200 EU/ml — no./total no. (%)	50/394 (13)	58/388 (15)	32/197 (16)	68/409 (17)	208/1388 (15)
<66.96 EU/ml — no./total no. (%)	142/394 (36)	144/388 (37)	66/197 (34)	146/409 (36)	498/1388 (36)
Median (IQR) — EU/ml	94 (43–149)	92 (45–145)	94 (46–143)	96 (47–156)	95 (46–148)
Geometric mean — EU/ml	85	87	91	90	88
Children					
No. of participants	403	407	202	389	1401
Age					
Median (IQR) — yr	8 (4–13)	9 (4–12)	8 (3–13)	8 (4–13)	8 (4–13)
Distribution — no. (%)					
1–4 yr	137 (34)	123 (30)	71 (35)	136 (35)	467 (33)
5–11 yr	127 (32)	146 (36)	65 (32)	129 (33)	467 (33)
12–17 yr	139 (34)	138 (34)	66 (33)	124 (32)	467 (33)
Female sex — no. (%)	186 (46)	185 (45)	85 (42)	182 (47)	638 (46)
Country — no. (%)					
Guinea	163 (40)	156 (38)	77 (38)	150 (39)	546 (39)
Liberia	64 (16)	66 (16)	33 (16)	55 (14)	218 (16)
Mali	95 (24)	94 (23)	46 (23)	91 (23)	326 (23)
Sierra Leone	81 (20)	91 (22)	46 (23)	93 (24)	311 (22)
Ebola IgG concentration†					
≥200 EU/ml — no./total no. (%)	43/398 (11)	47/401 (12)	19/200 (10)	54/386 (14)	163/1385 (12)
<66.96 EU/ml — no./total no. (%)	198/398 (50)	187/401 (47)	97/200 (48)	188/386 (49)	670/1385 (48)
Median (IQR) — EU/ml	67 (29–127)	74 (33–122)	69 (33–122)	71 (33–141)	70 (32–128)
Geometric mean — EU/ml	63	67	67	70	66

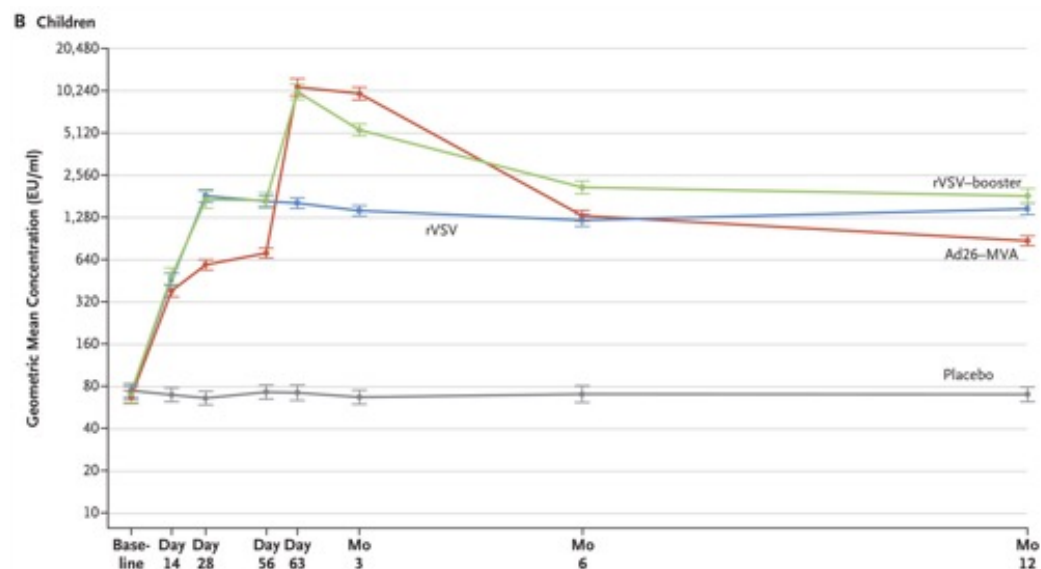
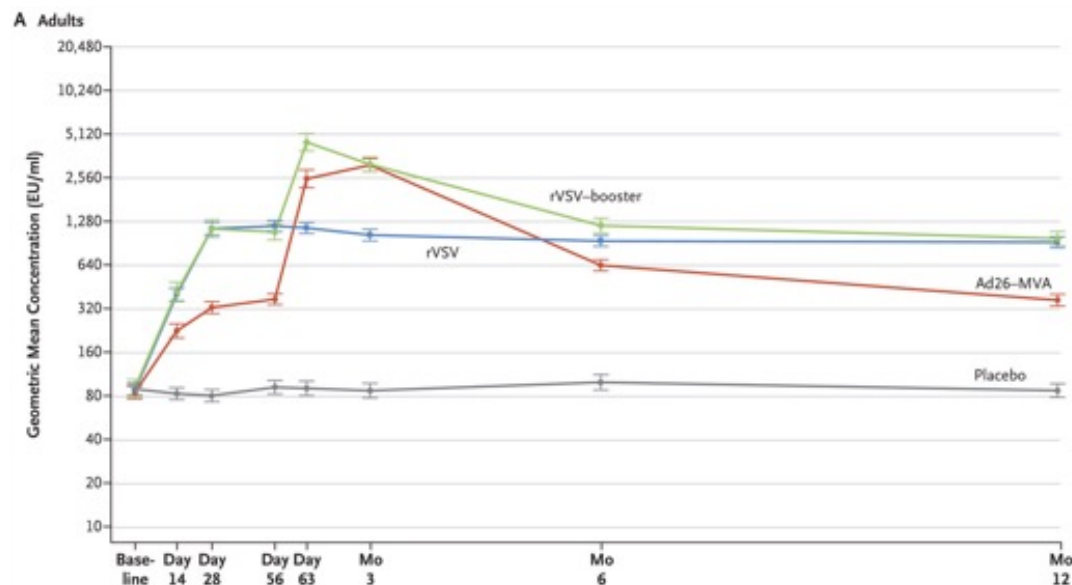
Injection-Site Reactions, Targeted Symptoms, and Serious Adverse Events.

Event	Ad26–MVA Group	Pooled rVSV Groups	rVSV Group	rVSV–Booster Group	Placebo Group
<i>number of participants with event/total number (percent)</i>					
Adults					
Injection-site reaction after first injection					
At 0–7 days	36/396 (9)†	133/592 (22)‡	—	—	21/412 (5)
At 14 days	2/387 (1)	1/579 (<1)	—	—	0/404
Symptoms after first injection					
At 0–7 days	198/396 (50)	390/592 (66)‡	—	—	182/412 (44)
At 14 days	92/387 (24)	133/579 (23)	—	—	100/404 (25)
Injection-site reaction after second injection					
At 56–63 days	49/380 (13)‡	—	12/365 (3)	20/187 (11)†	20/392 (5)
At 3 mo	0/369	—	1/356 (<1)	1/187 (1)	0/385
Symptoms after second injection					
At 56–63 days	124/382 (32)	—	127/373 (34)	76/188 (40)	127/398 (32)
At 3 mo	122/373 (33)	—	95/371 (26)	53/188 (28)	102/393 (26)
Serious adverse event or death§	14/396 (4)	—	6/395 (2)	1/197 (1)	5/412 (1)
Death	2/396 (1)	—	3/395 (1)	0/197	1/412 (<1)
Children					
Injection-site reaction after first injection					
At 0–7 days	59/403 (15)‡	126/609 (21)‡	—	—	19/389 (5)
At 14 days	1/397 (<1)	1/603 (<1)	—	—	0/380
Symptoms after first injection					
At 0–7 days	195/403 (48)	363/609 (60)‡	—	—	166/389 (43)
At 14 days	64/397 (16)	93/603 (15)	—	—	70/380 (18)
Injection-site reaction after second injection					
At 56–63 days	55/398 (14)‡	—	26/396 (7)	23/198 (12)‡	16/381 (4)
At 3 mo	0/392	—	0/392	0/197	0/378
Symptoms after second injection					
At 56–63 days	127/399 (32)	—	112/400 (28)	64/198 (32)	106/383 (28)
At 3 mo	85/393 (22)	—	93/396 (23)	41/198 (21)	90/380 (24)
Serious adverse event or death¶	5/403 (1)	—	9/407 (2)	3/202 (1)	8/389 (2)
Death	0/403	—	3/407 (1)	0/202	2/389 (1)

Geometric Mean Concentrations and Antibody Response According to Follow-up Visit.

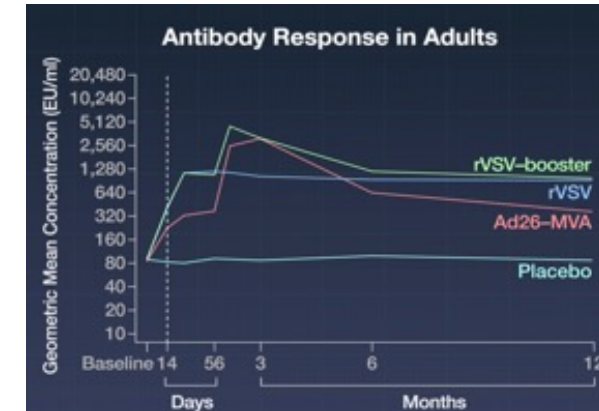
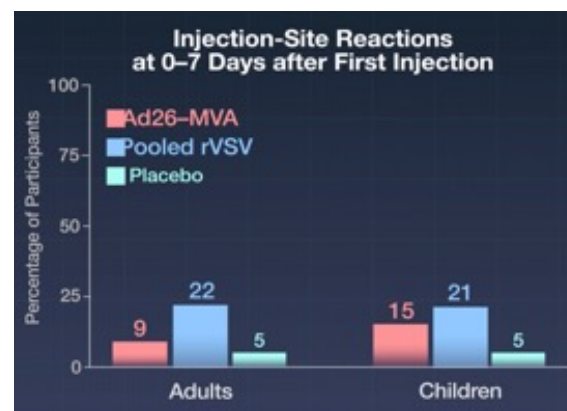
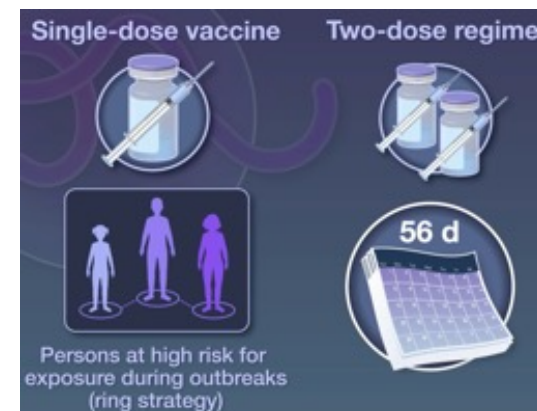
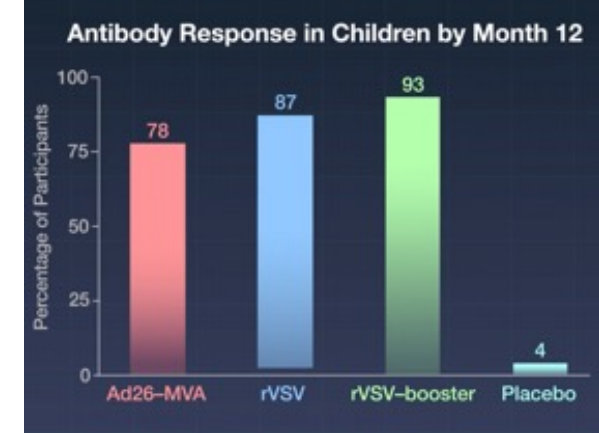
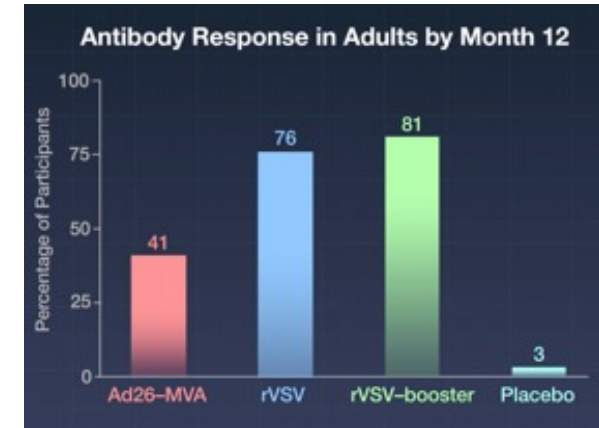
Variable	Ad26-MVA Group	Pooled rVSV Groups	rVSV Group	rVSV-Booster Group	Placebo Group
Adults					
At 7 days					
No. of participants	379	560	—	—	396
Geometric mean concentration (EU/ml)	87	91	—	—	79
Percentage of participants with response	2	2	—	—	1
At 14 days					
No. of participants	375	561	—	—	386
Geometric mean concentration (EU/ml)	244	428	—	—	89
Percentage of participants with response	22	44	—	—	1
At 28 days					
No. of participants	374	553	—	—	381
Geometric mean concentration (EU/ml)	355	1218	—	—	87
Percentage of participants with response	36	80	—	—	1
At 56 days					
No. of participants	369	541	—	—	364
Geometric mean concentration (EU/ml)	387	1193	—	—	96
Percentage of participants with response	41	84	—	—	2
At 63 days					
No. of participants	362	—	355	182	354
Geometric mean concentration (EU/ml)	2726	—	1243	4819	96
Percentage of participants with response	82	—	85	98	2
At 3 mo					
No. of participants	359	—	360	184	360
Geometric mean concentration (EU/ml)	3328	—	1084	3294	91
Percentage of participants with response	94	—	81	96	2
At 6 mo					
No. of participants	365	—	368	184	359
Geometric mean concentration (EU/ml)	666	—	973	1221	103
Percentage of participants with response	69	—	80	87	4
At 12 mo					
No. of participants	374	—	371	185	377
Geometric mean concentration (EU/ml)	401	—	992	1037	93
Percentage of participants with response†	41	—	76	81	3

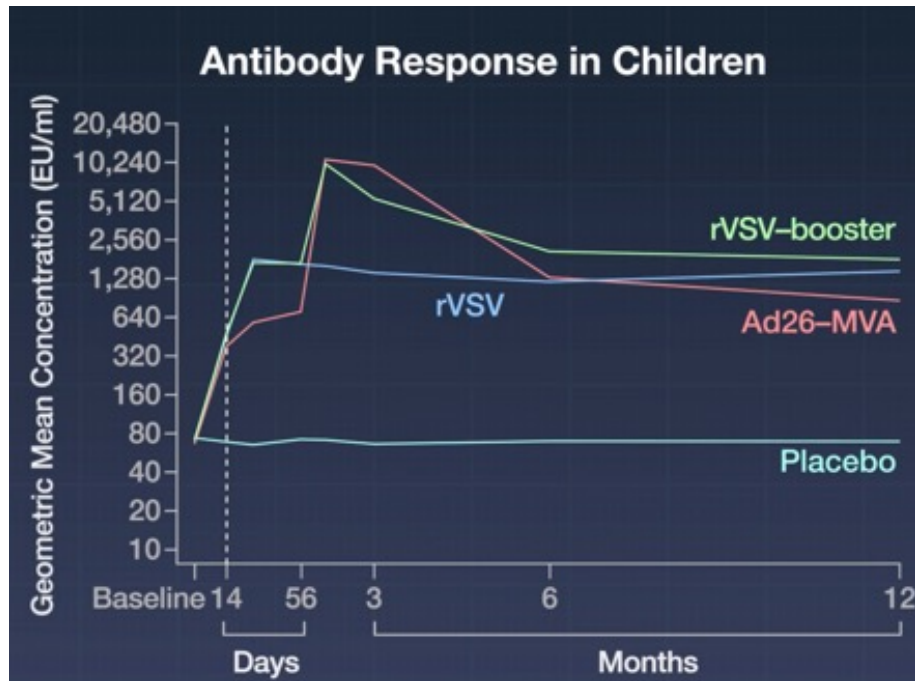
Variable	Ad26-MVA Group	Pooled rVSV Groups	rVSV Group	rVSV-Booster Group	Placebo Group
Children					
At 7 days					
No. of participants	379	571	—	—	365
Geometric mean concentration (EU/ml)	74	69	—	—	61
Percentage of participants with response	2	1	—	—	1
At 14 days					
No. of participants	382	586	—	—	372
Geometric mean concentration (EU/ml)	377	440	—	—	64
Percentage of participants with response	48	58	—	—	1
At 28 days					
No. of participants	389	580	—	—	369
Geometric mean concentration (EU/ml)	572	1688	—	—	62
Percentage of participants with response	66	90	—	—	1
At 56 days					
No. of participants	389	584	—	—	362
Geometric mean concentration (EU/ml)	679	1561	—	—	68
Percentage of participants with response	73	91	—	—	2
At 63 days					
No. of participants	382	—	392	186	356
Geometric mean concentration (EU/ml)	10,605	—	1560	9750	69
Percentage of participants with response	97	—	92	99	3
At 3 mo					
No. of participants	380	—	388	194	362
Geometric mean concentration (EU/ml)	9406	—	1351	5103	63
Percentage of participants with response	98	—	90	99	1
At 6 mo					
No. of participants	381	—	388	191	344
Geometric mean concentration (EU/ml)	1254	—	1153	1963	66
Percentage of participants with response	88	—	86	95	4
At 12 mo					
No. of participants	381	—	385	189	364
Geometric mean concentration (EU/ml)	828	—	1415	1745	67
Percentage of participants with response†	78	—	87	93	4



Antibody Response in Adults and Children (Geometric Mean Concentrations), According to Trial Visit.

The geometric mean concentration was based on a $\log_{10}$ concentration with baseline $\log_{10}$ titer and trial site as covariates. Antibody response was defined as an antibody concentration of at least 200 enzyme-linked immunosorbent assay units (EU) per milliliter and an increase from baseline in the antibody concentration by at least a factor of 4. Geometric mean concentrations are shown. I bars indicate 95% confidence intervals.





Discussion

These two trials provide immunogenicity and safety data for three Zaire Ebola vaccine regimens in adults and in children 1 year of age or older. By day 14 after the first injection, an antibody response was observed with both vaccines (i.e., Ad26.ZEBOV and rVSV). The peak percentage of participants with a response in each group was observed at month 3 (28 days after the receipt of the second dose) in the Ad26–MVA group among both adults and children, at day 28 in the rVSV group among both adults and children, and at day 63 among adults and at month 3 among children in the rVSV–booster group.

There is no universally agreed-on correlate of protective immunity to EVD, and in this trial we were unable to assess protection from disease given that there were no incident cases of EVD. However, it has been shown that levels of glycoprotein-binding antibodies strongly correlate with neutralizing antibody titers in nonhuman primates and humans. Moreover, the use of results from a clinical trial of a single dose of rVSVΔG-ZEBOV-GP, the threshold of 200 EU per milliliter, and an increase from baseline in the antibody concentration by a factor of 2 or more seem to be a reasonable correlate of protection.

Ebola vaccine strategies

- ✓ Showed no safety concerns
- ✓ Elicited antibody responses by day 14 that continued through month 12

Delirium in the Intensive Care Unit

Confusion Assessment Method für IMC (CAM-IMC)

Für nichtintubierte Patienten. Ein Delir liegt nur vor, wenn: 1, 2 und 3 oder 1,2 und 4 positiv sind.

1 Psychische Veränderung?

Akuter Beginn? (z.B. anders als vor ICU-Aufenthalt) ?
Ändert sich das Verhalten im Tagesverlauf ?

NEIN

STOP
Kein Delir

JA

2 Aufmerksamkeitsstörung

Lesen Sie dem Pat. folgende Buchstaben vor : **A N A N A S B A U M**

"Drücken Sie meine Hand, wenn ich ein "A" vorlese."

Fehler: Pat. drückt beim "A" nicht die Hand

Fehler: Patient drückt bei einem anderen Buchstaben als "A"

1 oder 2 Fehler

STOP
Kein Delir

3

Fehler oder mehr

3 Bewusstseinsveränderung ("aktuelle" RASS)

Nur falls RASS = 0 (wach & aufmerksam) weiter zur nächsten Stufe

Falls RASS nicht 0 ist

RASS
= 0

DELIR

4 Desorientierung

Nur bei Pat., die sich verbal äußern können. Fragen Sie nach:

- Alter ☐
- Geburtsdatum ☐
- Ort / Name des Krankenhauses ☐
- Aktuelles Jahr ☐

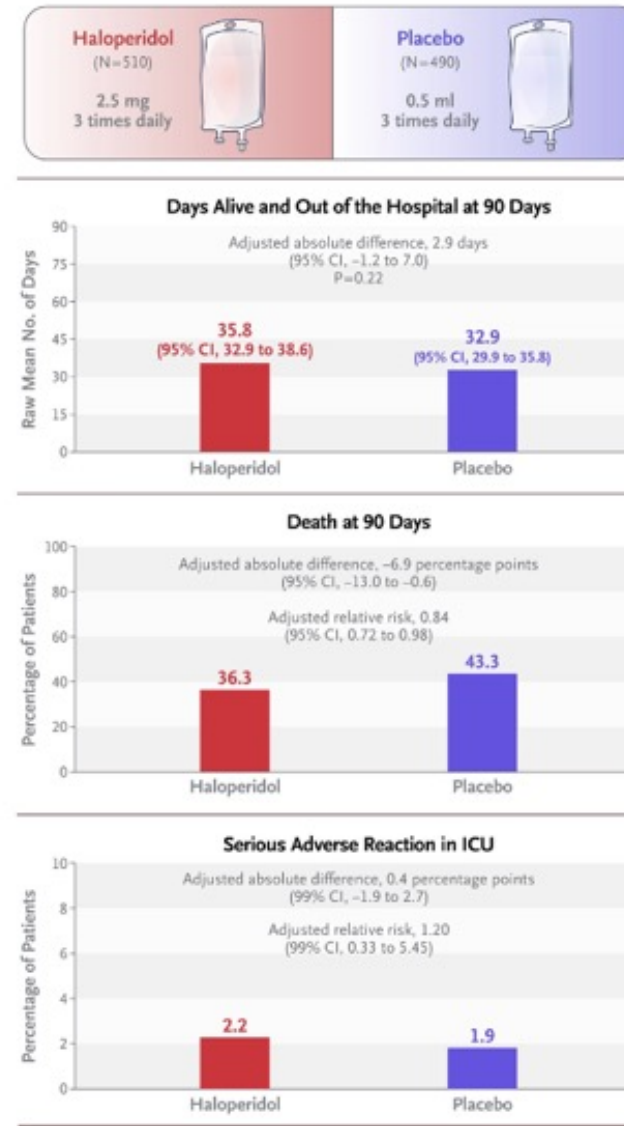
2 Fehler
oder mehr

1 Fehler

Kein Delir

Haloperidol for the Treatment of Delirium in ICU Patients

Haloperidol is frequently used to treat delirium in patients in the intensive care unit (ICU), but evidence of its effect is limited. In this multicenter, blinded, placebo-controlled trial, we randomly assigned adult patients with delirium who had been admitted to the ICU for an acute condition to receive intravenous haloperidol (2.5 mg 3 times daily plus 2.5 mg as needed up to a total maximum daily dose of 20 mg) or placebo. Haloperidol or placebo was administered in the ICU for as long as delirium continued and as needed for recurrences. The primary outcome was the number of days alive and out of the hospital at 90 days after randomization.



CONCLUSIONS

Among patients with delirium in the ICU, the use of haloperidol did not lead to a longer time alive and out of the hospital than placebo.

Trial Population

Patients 18 years of age or older who had been admitted to an ICU for an acute condition and had received a positive result on a screening test for delirium according to either the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) were assessed for eligibility. Patients were screened for delirium in the ICU at least twice daily by clinical staff using the tool that was standard at their site (either the CAM-ICU or ICDSC). Delirium was considered to be present if a patient had a positive CAM-ICU assessment or if four or more symptoms of delirium were present on the ICDSC assessment. We encouraged investigators and clinicians at the trial sites to screen all the patients fulfilling the inclusion criteria for enrollment in the trial. Patients could be assessed for eligibility throughout the entire ICU stay.

Trial Interventions

Enrolled patients were assigned to receive either intravenous haloperidol at a dose of 2.5 mg (0.5 ml of 5-mg-per-milliliter haloperidol solution) or 0.5 ml of placebo (isotonic saline) three times daily. At the discretion of the clinicians, additional as-needed doses could be administered up to a maximum total daily dose of 20 mg of haloperidol (4 ml of 5-mg-per-milliliter haloperidol solution) or 4 ml of placebo.

Characteristic	Haloperidol (N = 501)	Placebo (N = 486)
Median age (IQR) — yr	70 (62–76)	71 (63–76)
Female sex — no. (%)	177 (35.3)	161 (33.1)
Risk factors for delirium — no. (%)		
Traumatic brain injury within 6 mo	8 (1.6)	7 (1.4)
Stroke within 6 mo	12 (2.4)	17 (3.5)
History of mental illness	29 (5.8)	29 (6.0)
History of neurodegenerative disease	2 (0.4)	3 (0.6)
Active tobacco smoker	156 (31.2)	147 (30.2)
Alcohol overconsumption	85 (17.0)	77 (15.8)
Other substance abuse	9 (1.8)	9 (1.9)
Received benzodiazepines before hospitalization	13 (2.6)	17 (3.6)
Received benzodiazepines in hospital before randomization	166 (33.1)	143 (29.4)
Received haloperidol in hospital before ICU admission	34 (6.8)	33 (6.8)
Coexisting condition — no. (%)†		
Hematologic cancer	33 (6.6)	31 (6.4)
Metastatic cancer	15 (3.0)	15 (3.1)
Covid-19	37 (7.4)	52 (10.7)
Admission type — no. (%)		
Surgical	183 (36.5)	153 (31.5)
Medical	318 (63.5)	333 (68.5)
Use of organ support at randomization — no. (%)		
Mechanical ventilation‡	320 (63.9)	305 (62.8)
Vasopressors or inotropes§	272 (54.3)	239 (49.2)
Renal-replacement therapy¶	77 (15.4)	70 (14.4)
Predicted 90-day mortality — SMS-ICU score	34.7±15.4	34.6±15.4
Delirium motor subtype at randomization — no. (%)		
Hypoactive	277 (55.3)	263 (54.1)
Hyperactive	224 (44.7)	223 (45.9)
Delirium screening tool used — no. (%)		
CAM-ICU	385 (76.8)	382 (78.6)
ICDSC	116 (23.2)	104 (21.4)
Median time from hospital admission to ICU admission (IQR) — days	1.0 (0.0–5.0)	1.0 (0.0–5.0)
Median time from ICU admission to randomization (IQR) — days	3.9 (1.8–9.7)	4.1 (1.6–8.9)

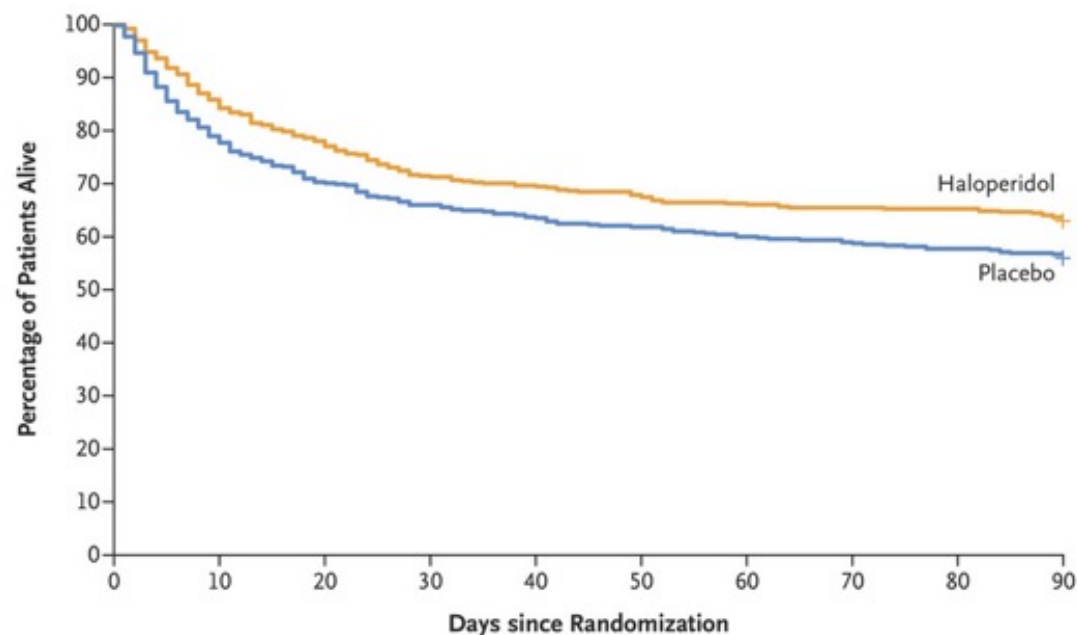
Use of Haloperidol or Placebo, Rescue Medication, Open-Label Antipsychotic Agents, or Restraint in the ICU after Randomization.

Variable	Haloperidol (N = 501)	Placebo (N = 486)
Median duration of trial intervention (IQR) — days	3.6 (1.8–6.8)	3.3 (1.8–6.2)
Median no. of daily doses received (IQR)†	3.4 (2.8–4.5)	3.6 (3.0–5.1)
Median total no. of doses received (IQR)	13.0 (7.0–26.0)	13.0 (7.0–26.0)
Median daily dose (IQR) — mg/day*	8.3 (6.8–11.4)	9.0 (7.4–12.5)
Median cumulative dose (IQR) — mg	32.5 (17.5–62.5)	32.5 (17.5–62.5)
Received one or more as-needed doses — no. (%)	364 (72.7)	358 (73.7)
Median total no. of as-needed doses received (IQR)	5.0 (2.0–10.0)	5.0 (3.0–12.0)
Use of rescue medication		
Propofol†		
No. of patients (%)	88 (17.6)	73 (15.0)
Median duration of use (IQR) — days	2.0 (1.0–4.3)	3.0 (1.0–4.0)
α_2 -agonist†		
No. of patients (%)	239 (47.7)	253 (52.1)
Median duration of use (IQR) — days	3.0 (2.0–5.0)	3.0 (2.0–5.0)
Benzodiazepines†		
No. of patients (%)	137 (27.3)	158 (32.5)
Median duration of use (IQR) — days	2.0 (1.0–4.0)	2.0 (1.0–4.0)
Use of open-label antipsychotic agents		
No. of patients (%)	66 (13.2)	63 (13.0)
Median duration of use (IQR) — days	3.7 (1.0–10.3)	3.0 (1.3–8.8)
Use of restraint during delirium — no. (%)	9 (1.8)	10 (2.1)

Primary and Secondary Outcomes.*

Outcome	Haloperidol	Placebo	Adjusted Absolute Difference (95% or 99% CI)†	Adjusted Relative Risk (95% or 99% CI)‡	P Value
Primary outcome					
Days alive and out of hospital at 90 days — raw mean no. (95% CI)‡	35.8 (32.9 to 38.6)	32.9 (29.9 to 35.8)	2.9 (−1.2 to 7.0)§	NC	0.22¶
Death — no./total no. (%)	182/501 (36.3)	210/485 (43.3)	−6.9 (−13.0 to −0.6)**	0.84 (0.72 to 0.98)	
Length of hospital stay — raw mean no. of days (95% CI)††	28.8 (26.7 to 30.8)	26.4 (24.4 to 28.5)	2.3 (−0.6 to 5.1)§	NC	
Secondary outcomes					
Days alive without delirium or coma — raw mean no. (99% CI)‡‡	57.7 (53.4 to 62.0)	52.6 (48.0 to 57.1)	5.1 (−1.2 to 11.3)§	NC	
Days alive without mechanical ventilation — raw mean no. (99% CI)	57.9 (53.7 to 62.2)	53.9 (49.5 to 58.3)	4.0 (−2.2 to 10.1)§	NC	
Serious adverse reaction in ICU — no./total no. (%)	11/501 (2.2)	9/486 (1.9)	0.4 (−1.9 to 2.7)**	1.20 (0.33 to 5.45)	
Use of rescue medication — no./total no. (%)§§	288/501 (57.5)	302/486 (62.1)	−4.0 (−11.8 to 3.6)**	0.93 (0.82 to 1.06)	
Days with use of rescue medication per patient — raw mean no. (99% CI)	2.9 (2.3 to 3.5)	2.9 (2.3 to 3.4)	0.1 (−0.7 to 0.9)	NC	

A Overall Survival



B Main and Subgroup Analyses of the Primary Outcome

Subgroup	No. of Patients		Mean No. of Days Alive and Out of Hospital (95% CI)		Adjusted Mean Difference (95% CI)
	Haloperidol	Placebo	Haloperidol	Placebo	
All patients	501	486	35.8 (32.9 to 38.7)	32.9 (29.9 to 35.8)	2.9 (0.5 to 5.3)
Motor subtype of delirium					
Hyperactive	217	216	39.3 (34.9 to 43.7)	34.9 (30.4 to 39.3)	4.4 (1.0 to 7.8)
Hypoactive	274	256	33.0 (29.3 to 36.8)	31.2 (27.3 to 35.1)	1.8 (0.1 to 3.5)
Age					
<69 yr	221	189	39.3 (35.2 to 43.4)	39.1 (34.5 to 43.8)	0.2 (-1.5 to 1.9)
≥69 yr	270	283	32.9 (29.0 to 36.9)	28.7 (24.9 to 32.4)	4.2 (1.3 to 7.1)
Sex					
Male	319	314	35.6 (32.1 to 39.1)	32.4 (28.8 to 36.0)	3.2 (0.3 to 6.1)
Female	172	158	36.2 (31.2 to 41.2)	33.8 (28.6 to 39.1)	2.4 (0.1 to 4.7)
Admission type					
Surgical	178	149	36.9 (32.4 to 41.5)	36.9 (31.9 to 42.0)	0.0 (-2.1 to 2.1)
Medical	313	323	35.2 (31.5 to 38.8)	31.0 (27.4 to 34.6)	4.2 (1.5 to 6.9)
Risk factors for delirium					
Yes	308	279	37.5 (33.9 to 41.1)	33.0 (29.2 to 36.8)	4.5 (1.6 to 7.4)
No	183	193	32.9 (28.2 to 37.6)	32.7 (27.9 to 37.4)	0.2 (-2.5 to 2.9)
SMS-ICU					
<25	383	361	38.5 (35.3 to 41.7)	35.3 (32.0 to 38.6)	3.2 (0.3 to 6.1)
≥25	108	111	26.3 (20.3 to 32.3)	25.1 (19.0 to 31.1)	1.2 (-1.1 to 3.5)

Placebo Better Haloperidol Better

Figure S3. Distribution of Days Alive without Delirium or Coma in the ICU

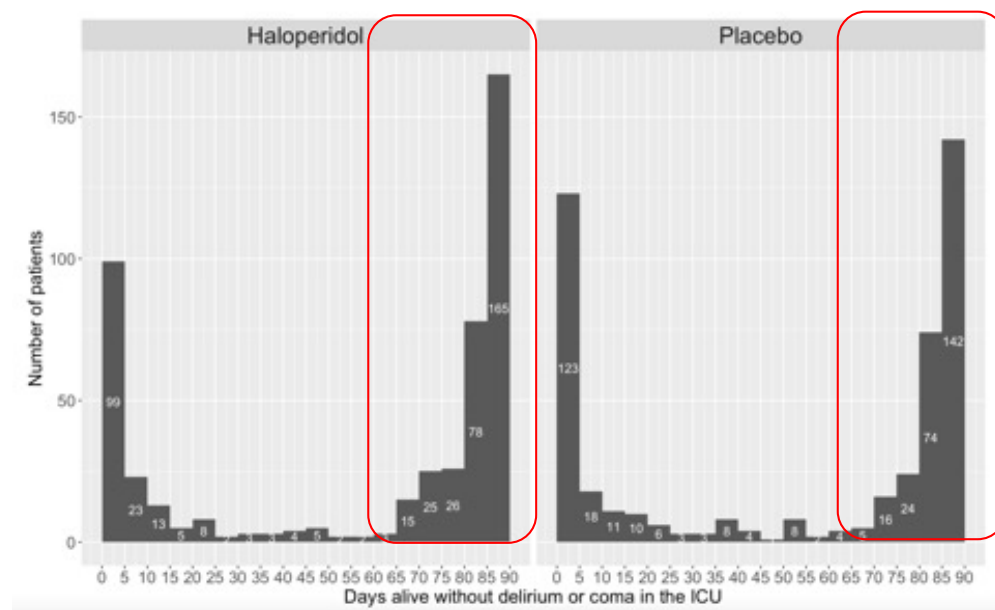


Figure S4. Distribution of Days Alive without Mechanical Ventilation

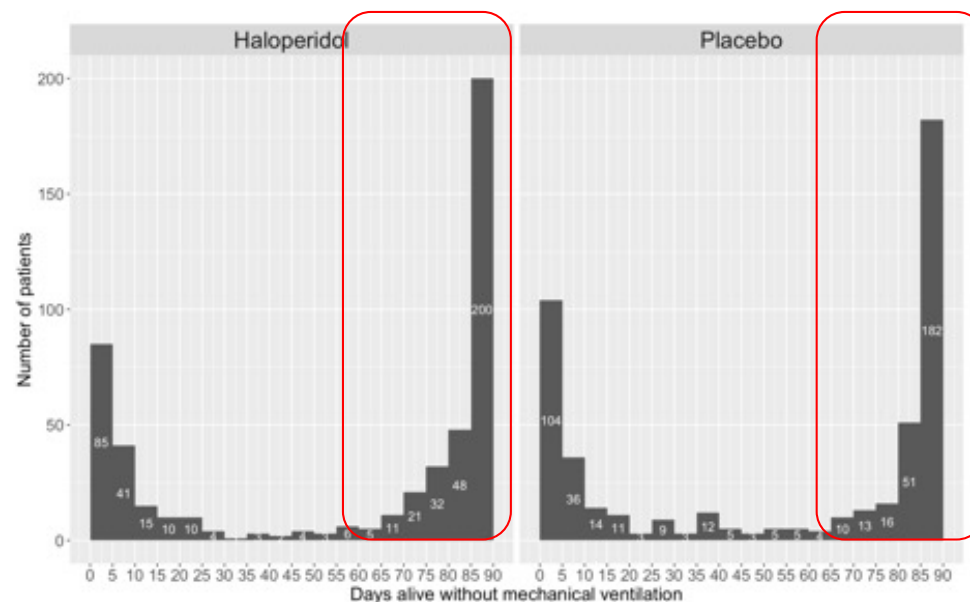
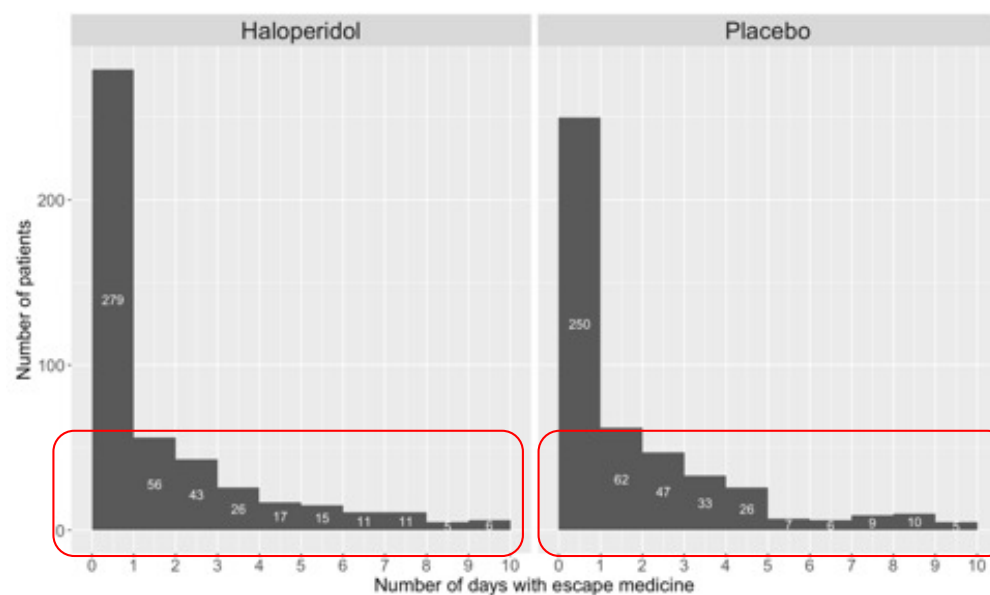
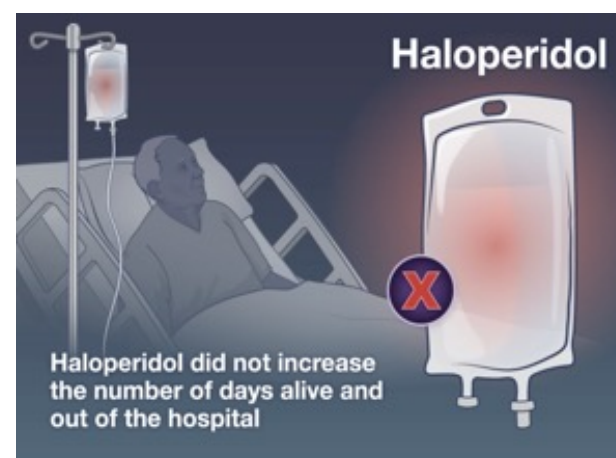
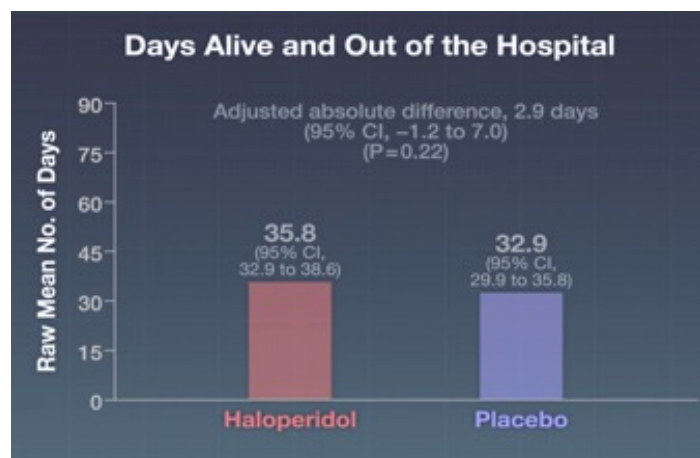
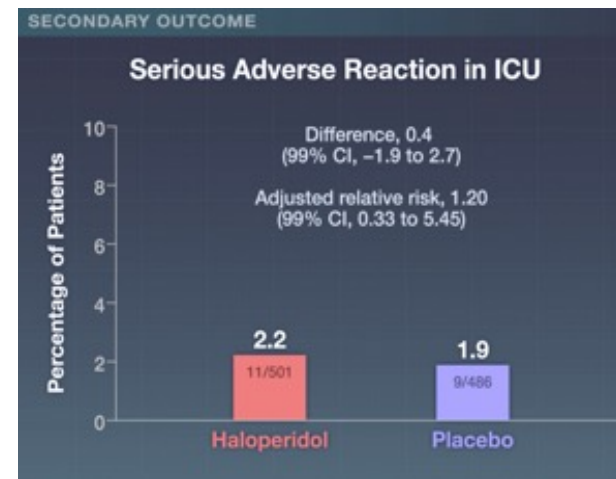
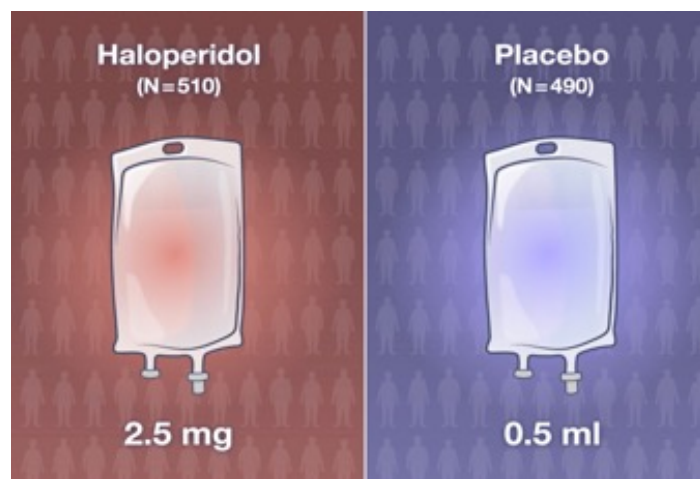
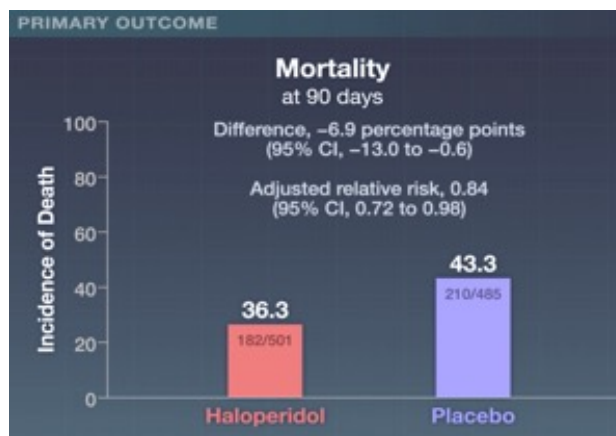


Figure S5. Distribution of Number of Days with Escape Medication





The trial has several limitations. The screening for delirium and eligibility that was performed by clinical staff probably resulted in some eligible patients being missed for inclusion and a lower enrollment of patients with hypoactive delirium than with hyperactive delirium. However, this screening process may have resembled clinical practice and ensured that patients could be enrolled after hours. The data on coexisting conditions beyond risk factors for delirium were sparse. The composite nature of the primary outcome may challenge the interpretation of the results, since the point estimate for mortality was lower and the point estimate for length of hospital stay was higher in the haloperidol group than in the placebo group. We did not collect detailed data on other sedatives, pain medications, or nonpharmacologic interventions administered to patients. Some patients were withdrawn from the trial (primarily owing to withdrawal of consent), which resulted in exposure to open-label antipsychotic agents in 13% of the trial population. However, the frequency of such withdrawal was similar in the two trial groups.

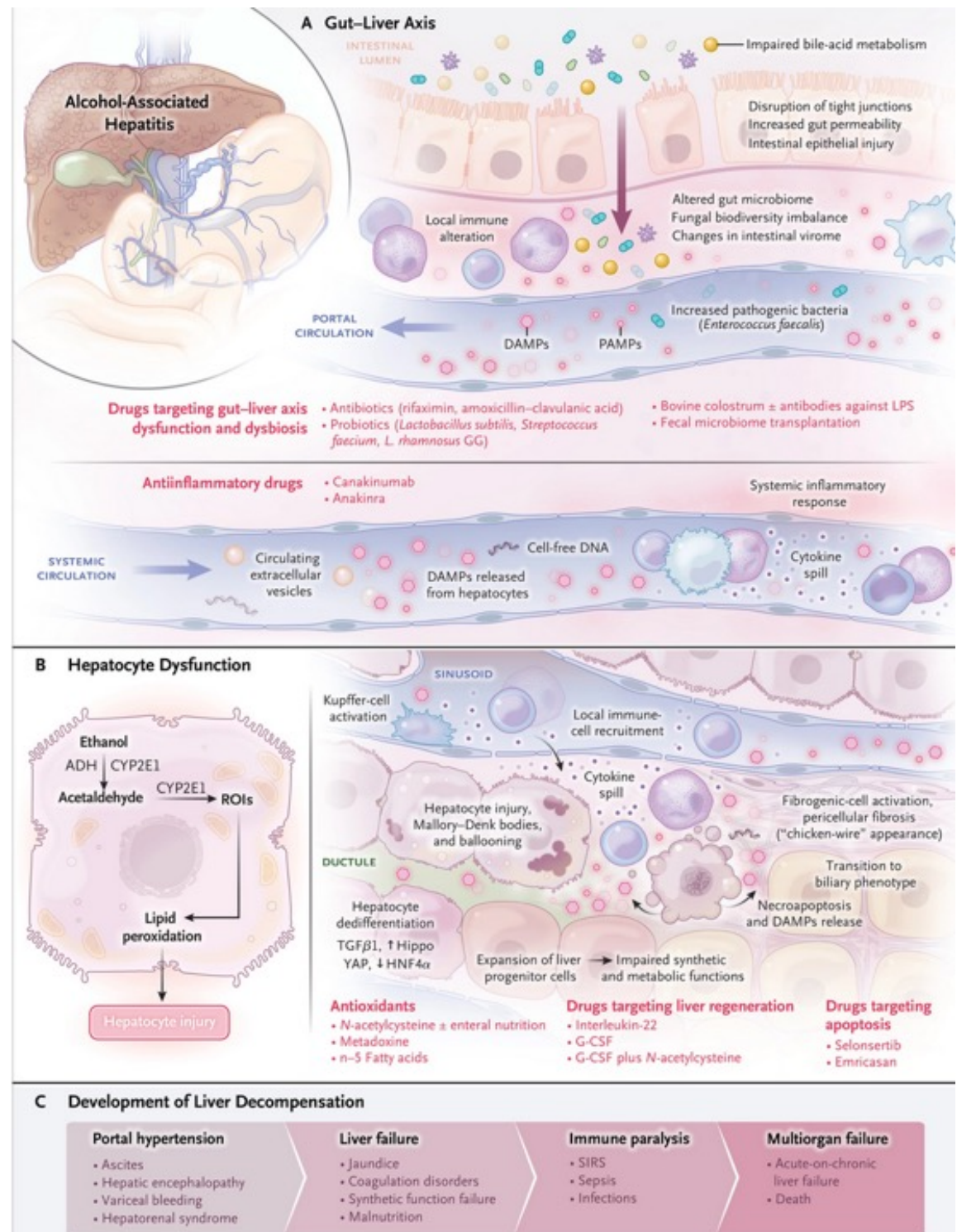
Alcohol-Associated Hepatitis

Alcohol use disorder is a major cause of advanced liver disease and liver-related hospitalization and death worldwide. Globally, alcohol is the cause of 50% of all deaths due to liver disease, and various forms of alcohol-associated liver disease (ALD) will develop in approximately 35% of patients with alcohol use disorder.³ The natural history of ALD is not well defined and is influenced by periods of heavy alcohol intake and abstinence. The clinical and histopathological forms of ALD range from isolated steatosis to progressive steatohepatitis with fibrosis accumulation to cirrhosis and its complications, culminating in the development of hepatocellular carcinoma. Young women constitute the fastest growing population assessed for liver transplantation in the United States, and female sex is independently associated with ALD-related burden and alcohol-related acute-on-chronic liver failure in the United States. Hispanic persons are predisposed to the development of alcohol-associated hepatitis, and genetic factors such as variations in the gene encoding patatin-like phospholipase domain-containing protein 3 (PNAPL3) influence disease severity among persons with alcohol-associated hepatitis.

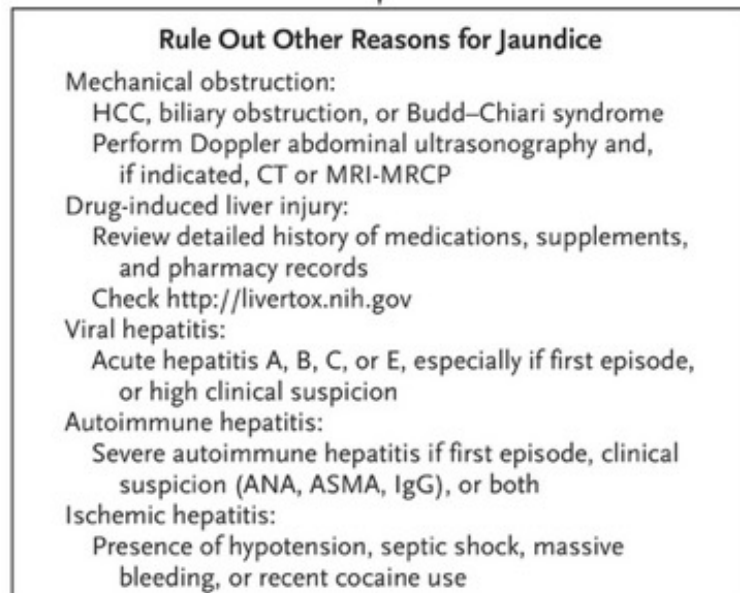
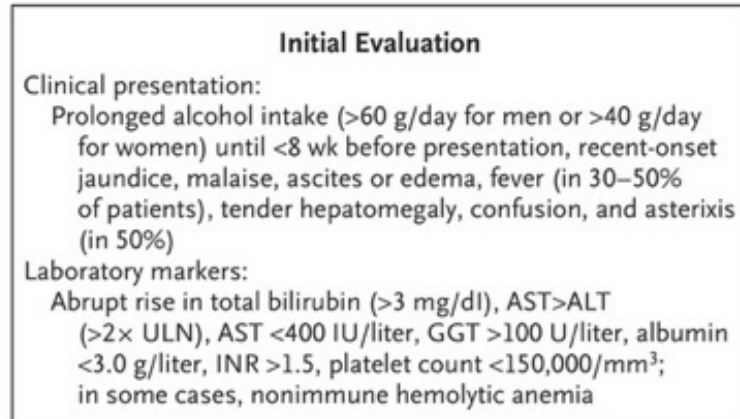
Earlier studies that focused on animal models that do not reproduce the main features of alcohol-associated hepatitis (i.e., hepatocellular failure and portal hypertension) proposed a central role for tumor necrosis factor α . Subsequent attempts to block this molecule in patients with alcohol-associated hepatitis were unsuccessful and were associated with severe and life-threatening infections, probably due to its role in liver regeneration and protection against bacterial infections.³¹ Translational studies have identified new potential cellular and molecular drivers of alcohol-associated hepatitis.

Pathogenesis of Alcohol-Associated Hepatitis.

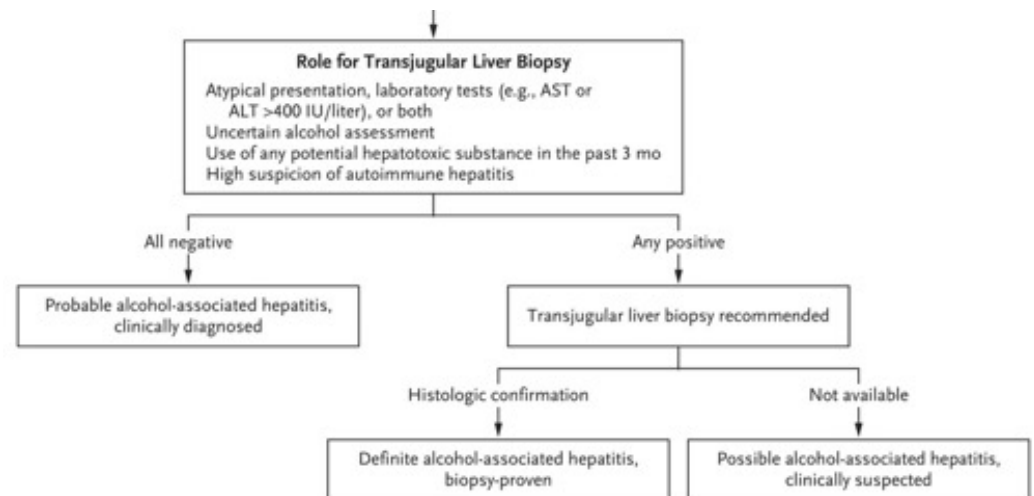
Panel A shows the role of the gut–liver axis; Panel B, the mechanisms involved in hepatocyte dysfunction; and Panel C, the development of liver-related decompensations and multiorgan failure. In Panels A and B, drugs and antioxidants that are being evaluated are shown in red. ADH denotes alcohol dehydrogenase, DAMPs danger-associated molecular patterns, G-CSF granulocyte colony-stimulating factor, HNF4 hepatocyte nuclear factor 4, LPS lipopolysaccharide, PAMPs pathogen-associated molecular patterns, ROIs reactive oxygen intermediates, SIRS systemic inflammatory response syndrome, TGF transforming growth factor, and YAP yes-associated protein.



Algorithm for the Diagnosis of Alcohol-Associated Hepatitis.

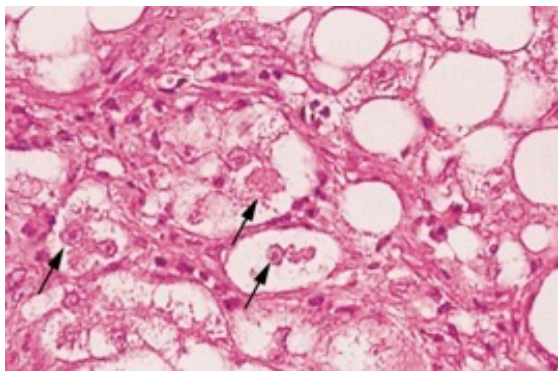


To convert the value for bilirubin to micromoles per liter, multiply by 17.1. ALT denotes alanine aminotransferase, ANA antinuclear antibodies, ASMA α -smooth-muscle actin antibodies, AST aspartate aminotransferase, CT computerized tomography, GGT γ -glutamyltransferase, HCC hepatocellular carcinoma, INR international normalized ratio, MRI-MRCP magnetic resonance imaging–magnetic resonance cholangiopancreatography, and ULN upper limit of the normal range.

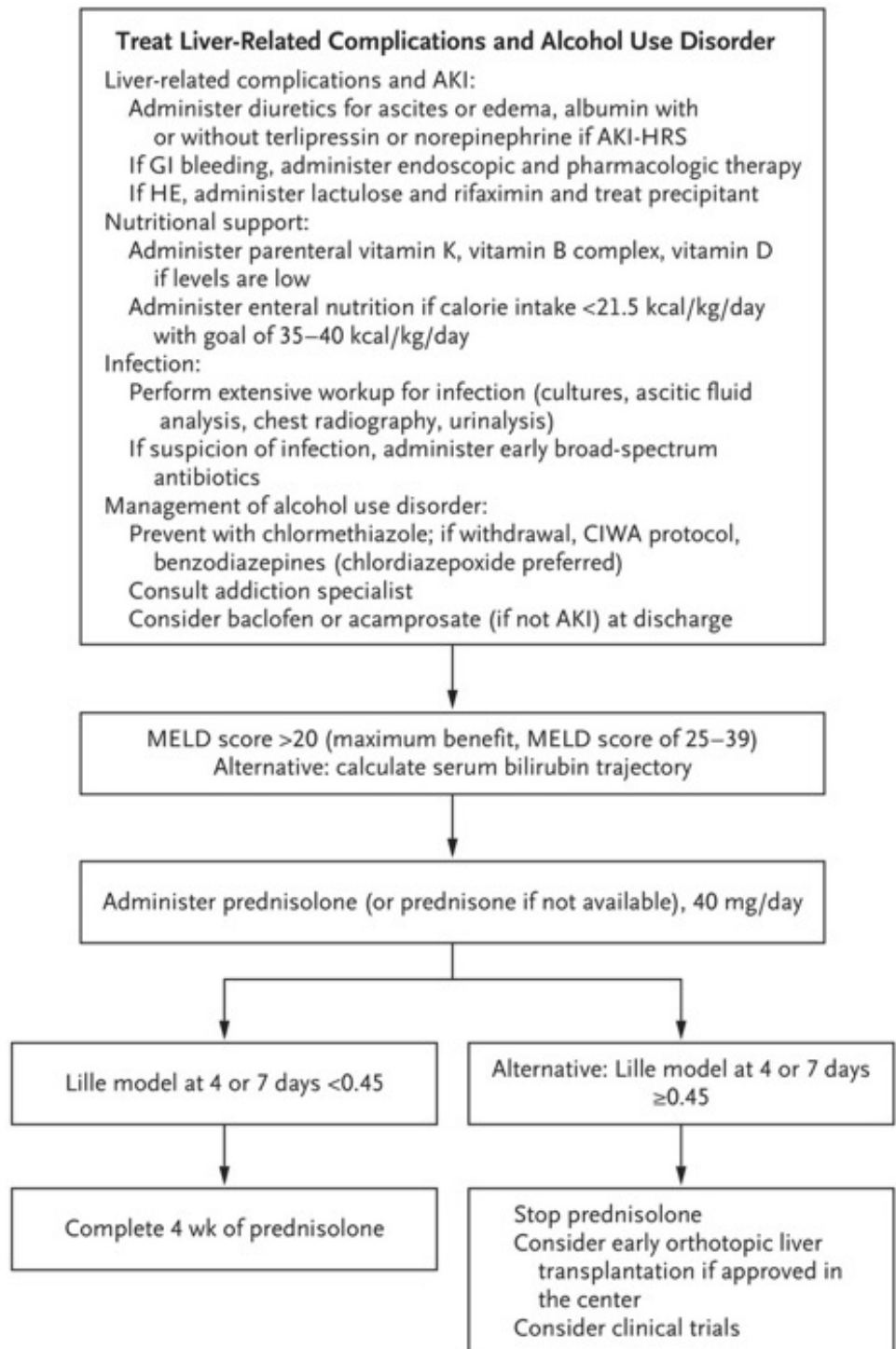


Algorithm for the Management of Alcohol-Associated Hepatitis.

Model for End-Stage Liver Disease (MELD) scores range from 6 to 40, with higher scores indicating a higher risk of death at 3 months. AKI denotes acute kidney injury, AKI-HRS AKI–hepatorenal syndrome, CIWA Clinical Institute Withdrawal Assessment for Alcohol, GI gastrointestinal, and HE hepatic encephalopathy.



Mallory-Körperchen **bestehen aus fehlgefalteten und zusammengelagerten Intermediärfilamenten, Ubiquitin und anderen Proteinen**. Sie treten u. a. bei alkoholischer und nichtalkoholischer Fettleberhepatitis, primär biliärer Cholangitis, Morbus Wilson oder medikamentös bedingt auf.



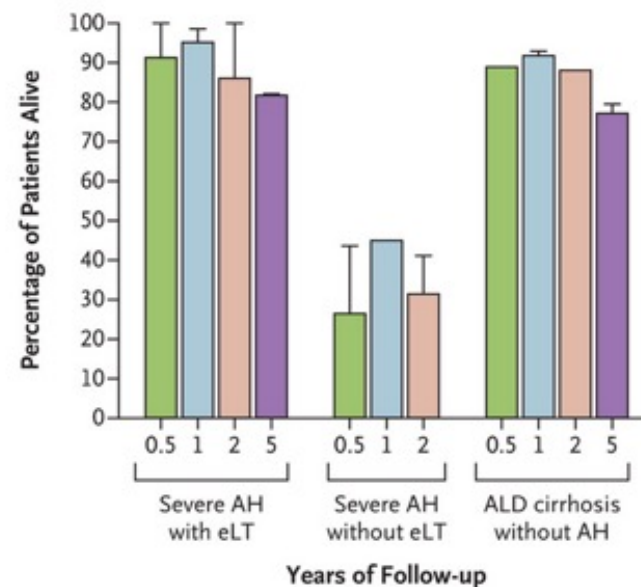
Summary of Studies Assessing Early Liver Transplantation (eLT) for Severe Alcohol-Associated Hepatitis (AH).

In Panels B and C, I bars indicate standard deviations. ALD denotes alcohol-associated liver disease, AUD alcohol use disorder, NIAAA National Institute on Alcohol Abuse and Alcoholism, and UNOS United Network for Organ Sharing.

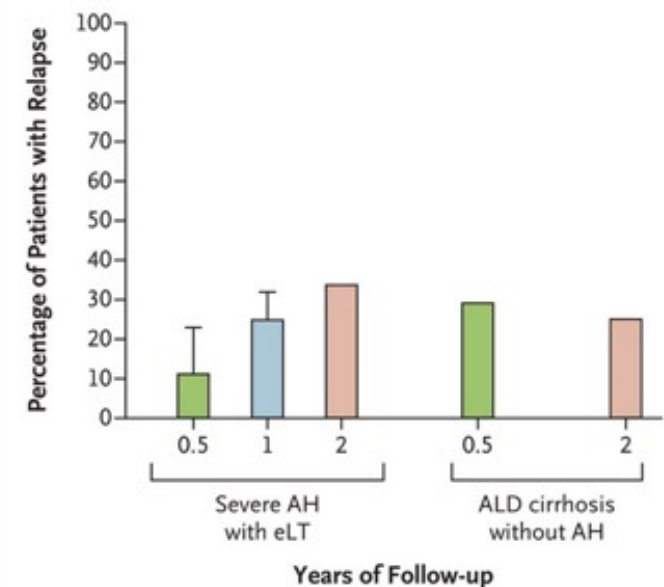
A Characteristics of the Studies

Study	Inclusion Criteria	Primary End Point	Location
Mathurin et al., 2011 ²¹	Severe AH not responding to glucocorticoids or rapid worsening of liver function No previous episodes of AH, supportive family members, no severe psychiatric conditions, commitment to alcohol abstinence	Survival at 6 mo	France Belgium
Im et al., 2016 ⁸⁵	Severe AH not responding to medical therapy	Survival at 6 mo	United States
Lee et al., 2017 ⁸⁶	Severe AH as first liver decompensation	Survival at 6 mo	United States
Lee et al., 2018 ⁸⁷	Severe AH and no previous diagnosis of liver disease or episodes of AH	Survival and AUD after liver transplantation	United States
Cotter et al., 2021 ⁸⁸	Severe AH and no previous diagnosis of liver disease or episodes of AH	Survival at 1 and 5 yr	United States
Lee et al., 2022 ⁸⁹	Retrospective analysis of UNOS database of patients undergoing liver transplantation for AH	Survival at 1 and 5 yr	United States
Louvet et al., 2022 ⁹⁰	Patients with severe AH who did not have a response to medical treatment and were eligible for eLT according to social and addiction evaluation	Alcohol relapse and survival at 2 yr	France Belgium
Germani et al., 2022 ⁹¹	Severe AH according to NIAAA criteria, not responding to medical therapy	Survival at 6, 12, and 24 mo	Italy

B Survival after Liver Transplantation in Patients with AH and ALD



C Alcohol Relapse after Liver Transplantation in Patients with AH and ALD



Future Directions

To reduce the burden of ALD including alcohol-associated hepatitis, excessive consumption of alcohol should be targeted with the use of a holistic societal approach; thus, more efficient public health policies are needed — for example, increasing taxes or raising the minimum price of a unit of alcohol. Furthermore, efforts must be aimed to assess the determinants of the increasing prevalence of ALD, in particular the severe forms in young women. In addition, to promote the development of new therapies, drug companies, regulatory agencies, and liver researchers should reach consensus on key determinants of outcomes and on the new end points for clinical trials. More translational research is needed to better characterize moderate alcohol-associated hepatitis and its early identification, to develop new prognostic biomarkers of alcohol-associated hepatitis, and to identify molecular subtypes for personalized medicine and response to therapy. The development of human-based experimental models could be useful to test new therapies. For patients who do not have a response to medical therapy, the timing and indications for early liver transplantation should be better defined. Digital transformation of health care offers care opportunities for ALD through remote health, analytics, and artificial intelligence techniques for the management of both alcohol use disorder and ALD. Finally, more efforts should be paid to define new holistic multidisciplinary approaches to treat the underlying alcohol use disorder and promote prolonged alcohol abstinence.

Case 40-2022: A 38-Year-Old Man with Exertional Chest Discomfort

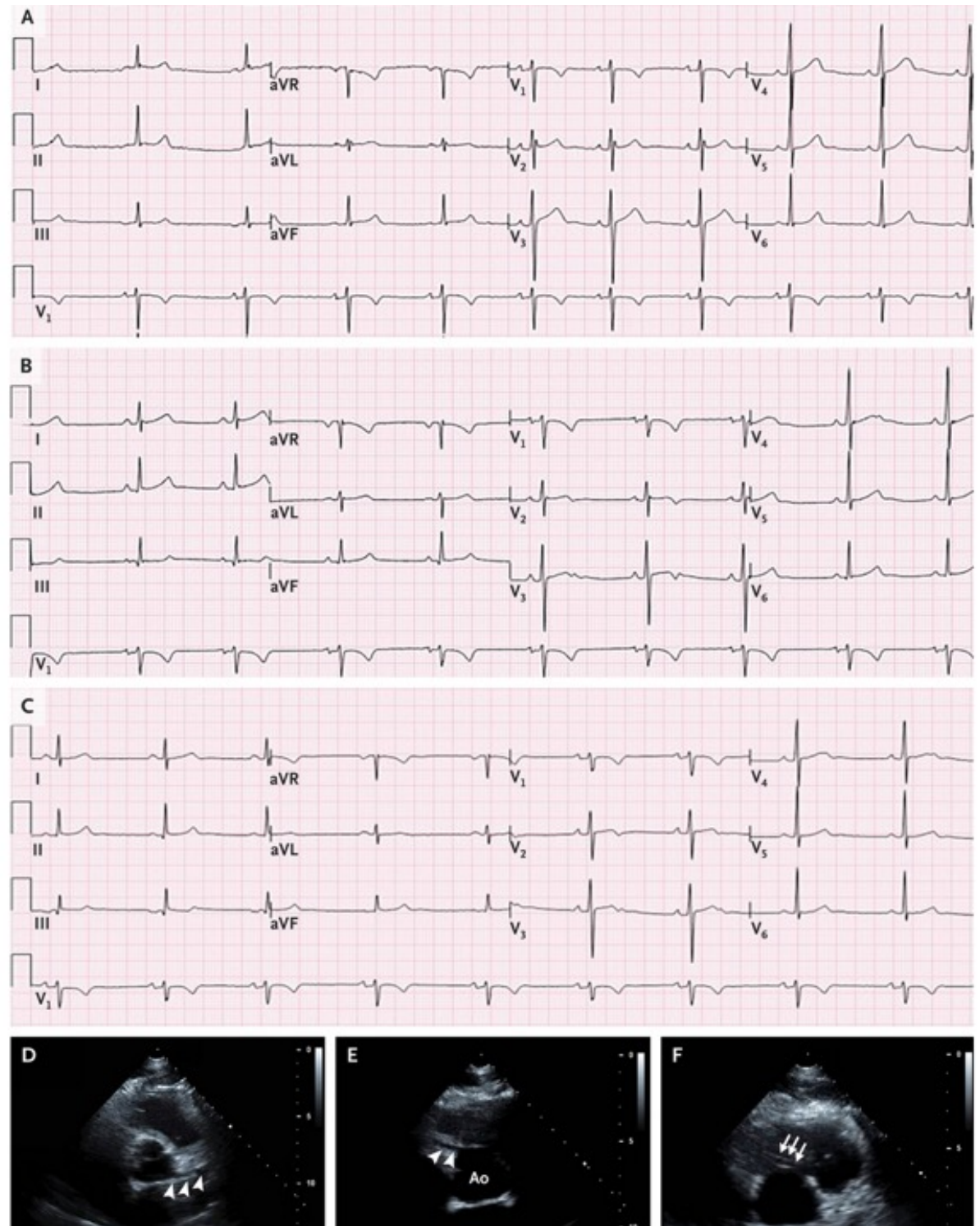
The patient had been a competitive athlete in the past and had remained an avid runner. Approximately 15 years before the current evaluation, while he was running, he had episodes of flushing with diffuse cutaneous swelling involving the face, lips, hands, and trunk, along with hives on the abdomen and legs and associated dyspnea. After the second episode, he lost consciousness while sitting on a bench. The next day, he was evaluated at an urgent care center. A Holter monitor was placed, and a transthoracic echocardiogram (TTE) was reportedly normal. The patient consulted with an allergist, who made a diagnosis of food-related exercise-induced anaphylaxis with reactions to soybeans, chickpeas, and tahini, on the basis of the foods he had eaten before these episodes and the results of radioallergosorbent testing. An epinephrine autoinjector was prescribed for use during future episodes, but the anaphylaxis symptoms did not recur. Approximately 4 months before the current evaluation, during a routine 5-mile jog, the patient had a new sensation that he described as “my heart beating out of my chest.” He rested, and the symptom subsided; he completed his run. One month later, during a bicycle ride, he had “crampy” discomfort in the anterior chest, which abated when he stopped cycling. Two weeks before the current evaluation, during a jog of several miles, he had cramping pain in the anterior chest on the left side that gradually escalated over a 5-minute period. He started walking, and the pain abated; he ran for an additional 20 minutes without a recurrence of pain. He sought an evaluation in the cardiology clinic of this hospital to determine the cause of his symptoms and the safety of continued vigorous exercise.

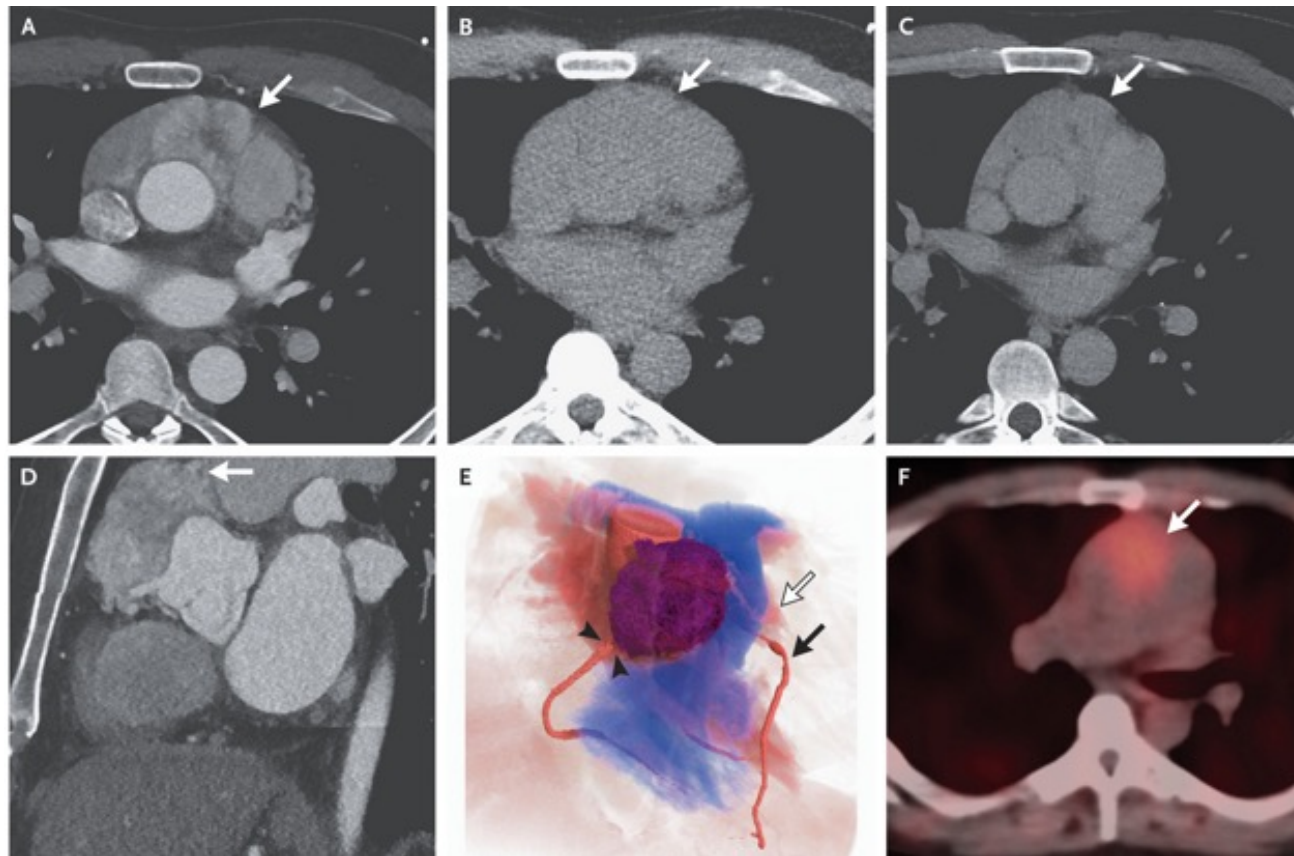
On evaluation in the cardiology clinic, a review of systems was negative for dyspnea, recent syncope, orthopnea, edema, cough, hemoptysis, and recent allergic symptoms. The patient ran or cycled four times per week and had previously completed a marathon. Five years earlier, an episode of syncope had occurred in the context of multiple episodes of nonbloody diarrhea, abdominal discomfort, and chills.

Electrocardiograms and Transthoracic Echocardiograms.

Electrocardiograms (ECGs) were obtained 15 years before the current presentation (Panel A), 5 years before the current presentation (Panel B), and at the time of the current presentation (Panel C). Anterior T-wave abnormalities from V₁ to V₃ are present on the ECG obtained at the time of the current presentation and on the ECG obtained 5 years earlier but not on the ECG obtained 15 years earlier.

Transthoracic echocardiograms obtained in the parasternal short-axis view of the heart show normal origins of the left coronary artery (Panel D, arrowheads) and of the right coronary artery (Panel E, arrowheads), as well as another vessel anterior to the aorta with an unclear origin (Panel F, arrows). Ao denotes aorta.



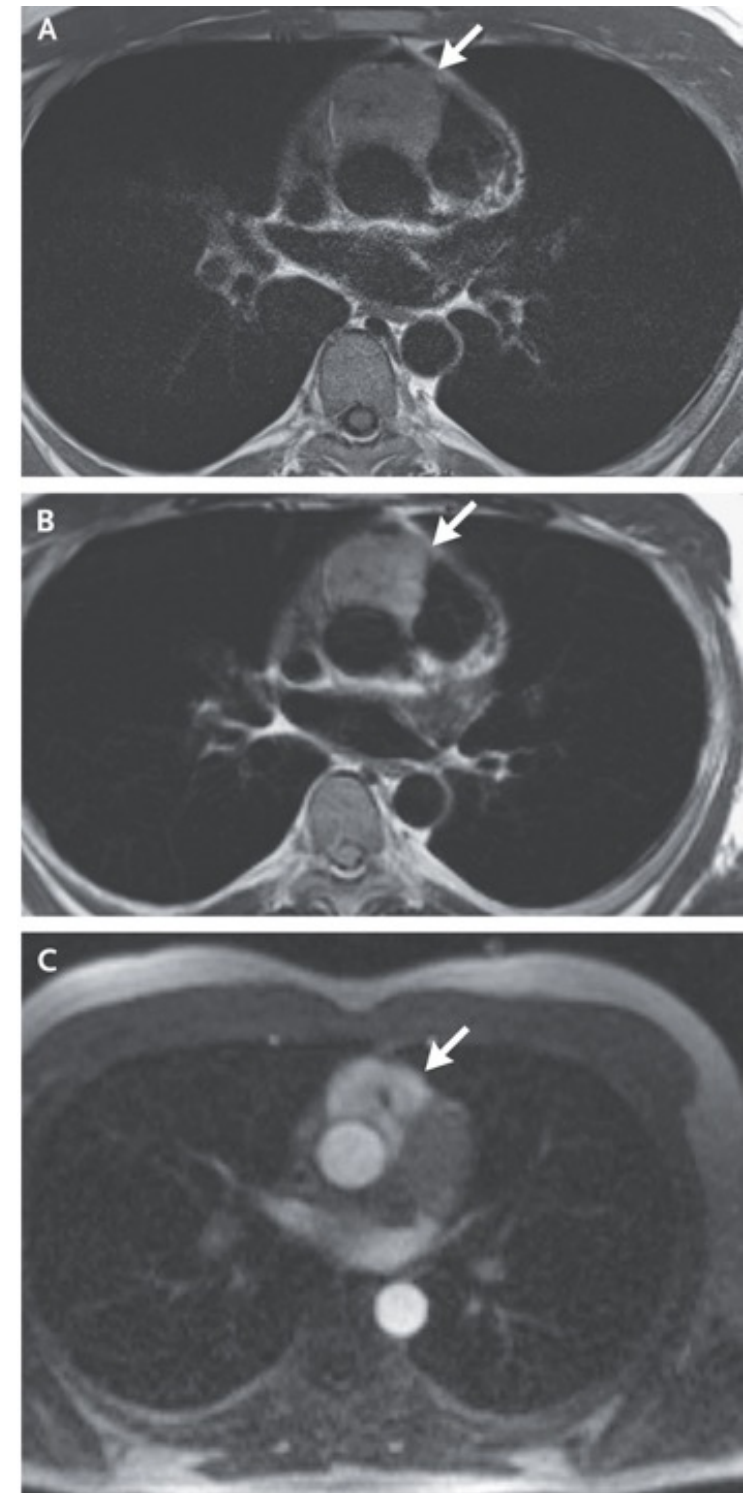


Coronary CT Angiogram and ^{123}I -MIBG SPECT Image. An axial CT image obtained during the arterial phase (Panel A) shows an intrapericardial mass (arrow), anterior to the heart and within the aortopulmonary groove, with heterogeneous enhancement and an attenuation level of 218 Hounsfield units (HU). The attenuation level of the mass is 50 HU on an image obtained before the administration of contrast material (Panel B, arrow) and 111 HU on an image obtained during the delayed phase (Panel C, arrow). A sagittal CT image (Panel D) shows that the proximal right coronary artery is encased by the mass (arrow). A volume-rendered image (Panel E) shows the relationship of the mass (in purple) with the chambers on the right side (in blue) and on the left side (in red) and with the coronary arteries; there is evidence of narrowing of the left anterior descending coronary artery (black arrow), prominent venous drainage (white arrow), and feeding vessels arising from the right coronary artery (arrowheads). An axial image from ^{123}I -metaiodobenzylguanidine (^{123}I -MIBG) single-photon-emission CT (SPECT) (Panel F) shows moderate tracer uptake in the mass (arrow).

Cardiac MRI.

On a T1-weighted image (Panel A), the heterogeneous mass is predominantly isointense (arrow). On a T2-weighted image (Panel B), the mass is hyperintense with punctate foci of hypointensity, which results in a “salt and pepper” appearance (arrow). On a first-pass perfusion image obtained after the administration of gadolinium-based contrast material (Panel C), enhancement is intense and brisk (arrow).

The first line of testing to rule out pheochromocytoma and paraganglioma is the measurement of plasma free metanephrines. In this patient, plasma and urinary metanephrine levels were normal. However, when clinical suspicion is high, comprehensive interrogation of catecholamine metabolism may be helpful. Although the urinary norepinephrine and epinephrine levels were not elevated in this patient, the plasma dopamine level was markedly elevated, at 1254 pg per milliliter (reference value, <30). Dopamine-secreting and dopamine-predominant paraganglioma is a rare subtype of paraganglioma. Patients may present with symptoms associated with vasodilatory dopamine excess, such as dizziness, vomiting, and flushing. These symptoms are particularly likely to occur when epinephrine and norepinephrine cosecretion is absent. In this patient with episodic exertional chest discomfort, a flushing syndrome 15 years earlier, and an intracardiac mass, we hypothesized that intratumoral metabolism may have been altered over time and become restricted to dopamine production.

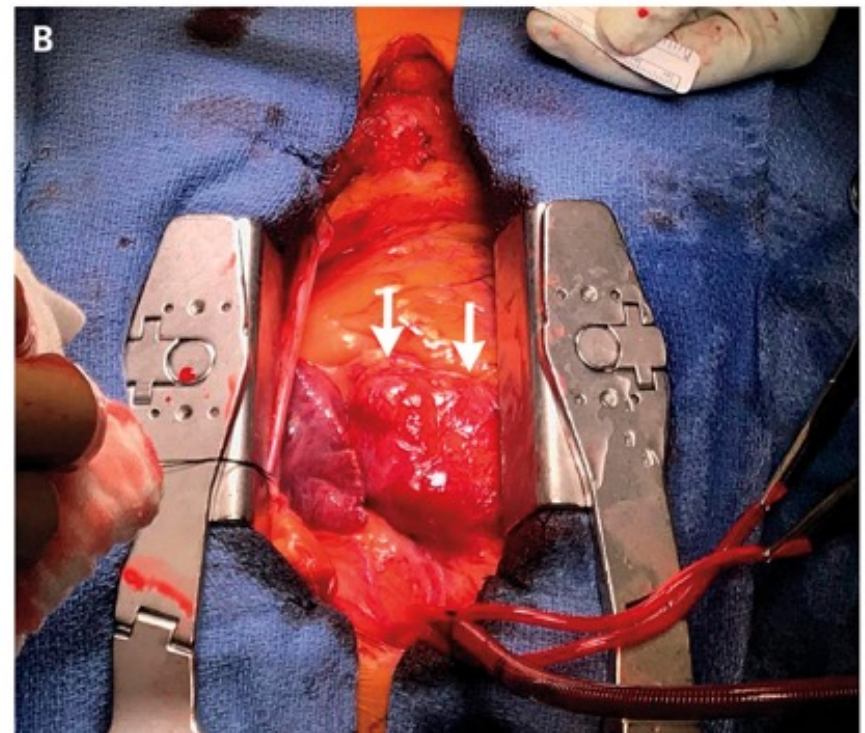
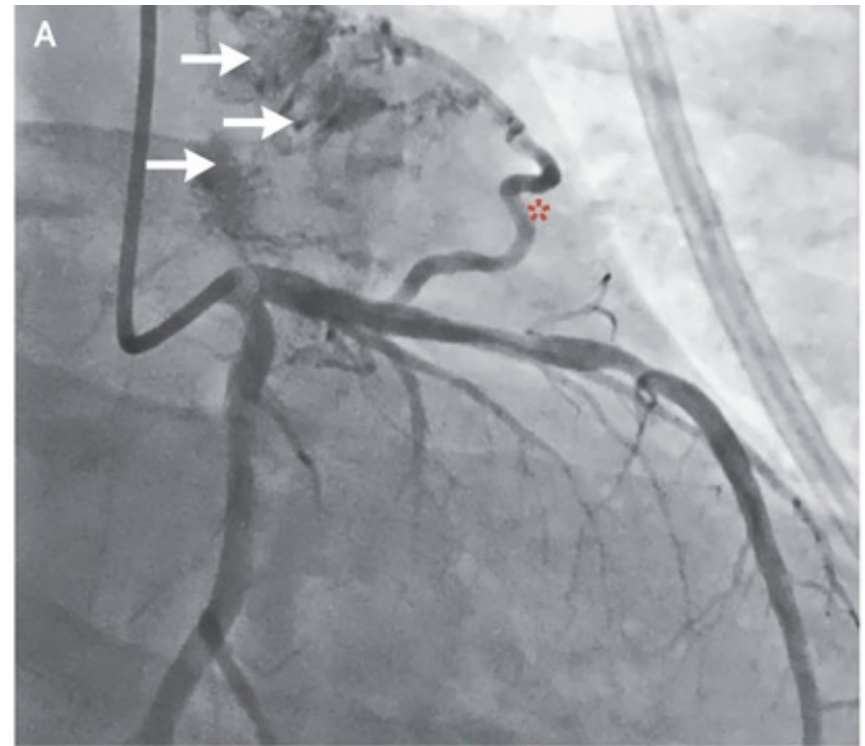


Coronary Angiogram and Photograph Obtained at Surgery.

A coronary angiogram (Panel A) shows multiple feeding vessels, including one dominant collateral vessel (asterisk) arising from the left coronary artery and supplying the tumor. There is a multilobed tumor blush (arrows). A photograph obtained during the surgical procedure (Panel B) shows the tumor (arrows) anterior to the aorta.

During the surgery, we made an effort to preserve the native aortic root by peeling the tumor off the wall of the aorta. However, the margins proved to be positive for tumor cells, so we performed a more radical operation, which involved resecting the sinuses of Valsalva and the aortic valve. The aortic root was reconstructed with a mechanical valve conduit.

Preoperative coronary imaging had shown proximal narrowing of the left anterior descending coronary artery; the left internal thoracic artery was used to bypass the stenosis. The proximal right coronary artery was encased by the tumor and was sacrificed in a planned manner. Coronary reconstruction was performed with a segment of saphenous vein, rather than with a segment of right internal thoracic artery; if the right internal thoracic artery is required to carry the entire circulatory load until the vessel has dilated and matured, hypoperfusion can occur. The tumor involved the anterior right ventricular outflow tract, which was excised and reconstructed with a bovine pericardial patch.

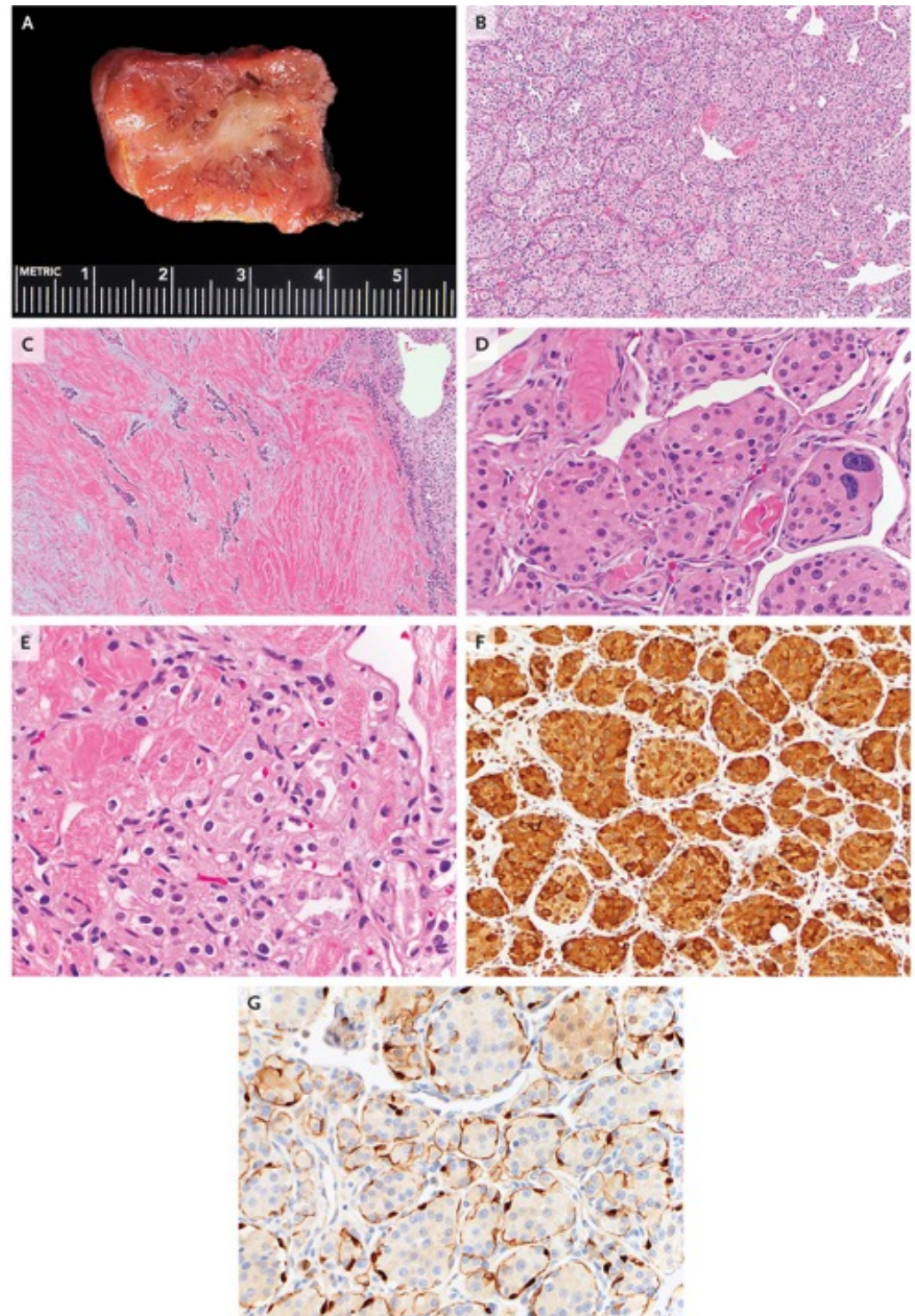


Specimen of the Resected Mass.

A section of the gross specimen (Panel A) shows central fibrosis and the black-inked resection margin. Hematoxylin and eosin staining shows Zellballen architecture (Panel B), sclerosis with infiltrating nests of tumor cells (Panel C), scattered tumor cells with marked endocrine atypia (Panel D), and cardiomyocytes infiltrated by tumor cells (Panel E). A stain for chromogranin A is strongly positive in tumor cells (Panel F). An S100 stain highlights sustentacular cells (Panel G). Given that up to 40% of patients with paraganglioma have a familial syndrome, genetic testing is recommended for all affected patients to determine the approach to monitoring. If the genetic testing is positive, the patient would undergo long-term screening tailored to the specific familial syndrome. [This patient was found to have a germline mutation in the gene encoding succinate dehydrogenase subunit C \(SDHC\), which is associated with familial paraganglioma syndrome 3.](#)

Final Diagnosis

Cardiac paraganglioma with a germline mutation in the gene encoding succinate dehydrogenase subunit C (*SDHC*).



A woman flew her dog to Nashville. Bluebell landed in Saudi Arabia instead.



“Well, your dog’s okay, but we think she’s been sent to Saudi Arabia,” the staff member said.

Miller felt like she couldn’t breathe. She and her husband, James, were moving from Britain to Nashville and had arranged for their dog, Bluebell, to be flown in the cargo hold of a British Airways flight. Because none of the Britain-based airlines they considered with flights to Nashville allowed animals in the cabin, it had been their only option. But, instead of putting Bluebell on the plane to Tennessee, crews accidentally shipped the black Labrador mix to Riyadh, Saudi Arabia, Miller told The Washington Post.